RESEARCH HORIZONS

In this issue

CANCER

plus news and views from across the University

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A warm welcome to Research Horizons magazine. This issue we focus on cancer – a significant research theme across many departments in the University and a clinical and healthcare strength within the Cambridge University Hospitals NHS Foundation Trust.

In the past decade, over £70 million has been invested in new cancer research buildings and facilities in Cambridge, including the Cancer Research UK Cambridge Research Institute (CRI)/Li Ka Shing Centre, the Strangeways Research Laboratory and the Hutchison/Medical Research Council Research Centre, as well as in new clinical facilities for cancer patients; and annual cancer research funding in Cambridge now exceeds £40 million. Professor Sir Bruce Ponder, featured on our front cover, leads the CRI, which hosts 250 scientists working within 21 research groups and is one of the principal cancer research facilities in Europe.

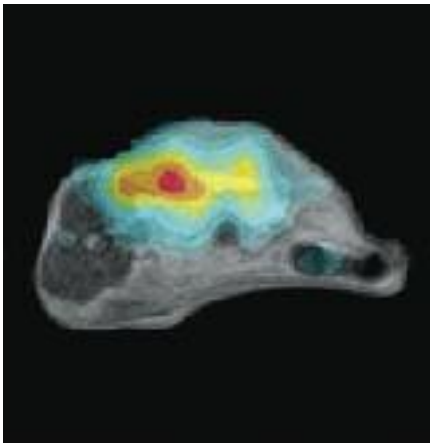
We hope that our Spotlight section gives a sense of the partnerships that are proving vital for translating cancer research into real benefits for patients: from understanding the fundamental basis of cancer, to identifying those individuals with the highest risk; and from diagnosing and treating cancer early, to moving towards tailored treatment and monitoring of patients. Helping to connect this research community, a virtual Cambridge Cancer Centre was launched in 2006 by Professor Ponder to promote interactions between researchers and clinicians working in diverse areas to achieve the best possible results for cancer patients.

Elsewhere in this issue, we bring you examples of some of the other remarkable research happening across the University, on areas as diverse as the swine flu pandemic, how Britain became an island nation, handwriting in 500-year-old manuscripts, dyslexia and dyscalculia, the purity and linguistic correctness of the French language, and the publishing of bestsellers.

If you have any comments and suggestions for future issues, please email them to me at Research.Horizons@admin.cam.ac.uk

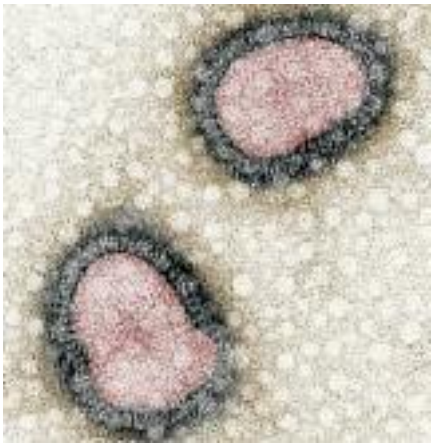
Louise Walsh

Dr Louise Walsh
Editor



PROFESSOR KEVIN BRINDLE

Watching cancer cells eat, breathe and die



DR PAUL DIGARD, DEPARTMENT OF PATHOLOGY

From pandemic to policy: combating swine flu

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New funding to untangle Alzheimer's disease

A major new drive to understand, diagnose and treat Alzheimer's disease has begun in Cambridge.

PROFESSOR PETER ST GEORGE-HYSLOP

Brain of an Alzheimer's patient (left), showing considerable cell loss, compared with a normal brain (right)

Funding from the Wellcome Trust (WT) and Medical Research Council (MRC) has been announced for a £5 million research programme on Alzheimer's disease (AD) in Cambridge. The programme, which is led by Professor Peter St George-Hyslop in the Cambridge Institute of Medical Research and Department of Clinical Neurosciences, is a major collaborative effort involving 15 scientists from seven research departments across Cambridge. The programme also involves scientists from the University of Bristol, the Max Planck Centre for Structural Molecular Biology in Germany and the University of Toronto in Canada.

AD is an increasingly common neurodegenerative disease of the brain that affects individuals in mid-to-late life, impairing intellectual function and memory. The disease, which is incurable, results when certain proteins in the brain become misfolded and form tangled masses that are toxic. The resulting progressive loss of cells in the brain gradually incapacitates patients for up to a decade before death. The incidence of AD is on the increase as populations live longer: in the UK, 700,000 people currently live with dementia, half of whom have AD; in 30 years' time, the estimates are that this number will have hit 1.4 million and be costing the UK economy £50 billion per year.

Professor St George-Hyslop explained the unique challenge the disease poses: 'Although AD has been known about for over a century, it's such a complex disease that attempts to understand the underlying mechanism using conventional tools have yielded confusing and conflicting answers. As a consequence, there is currently no drug that can halt its progression.'

To plug the gaps in knowledge, the interdisciplinary research programme builds on a collaboration that has been growing for several years in Cambridge, as co-investigator Professor Chris Dobson from the Department of Chemistry explained: 'A fascination with how the fundamental molecular events that underlie AD relate to what is happening in living systems has brought together a group of people with interests that range from theory to therapy.' The consortium pulls in expertise from biochemistry, genetics, clinical neuroscience, medical genetics, chemistry, chemical engineering, neurophysiology, physics, biophysics and pathology.

The programme aims to lay the basis for both the development of biological markers to detect disease at an early stage, before widespread damage has occurred, and the creation of effective therapeutics. 'Already, the consortium is working well. The atmosphere takes alight as people throw in ideas about novel experimental approaches using tools from both physical and life sciences that would not have been possible until very recently,' said Professor St George-Hyslop.

Professor Patrick Sissons, Head of the School of Clinical Medicine and Regius Professor of Physic, added: 'This initiative exemplifies the power of collaboration between internationally leading investigators who can look beyond their individual spheres, and work at the boundaries of traditional disciplines to bring new insight to a notoriously complicated disease.'

For more information, please contact Professor St George-Hyslop (phs22@cam.ac.uk).

Professor Lynn Gladden: Cambridge's new Pro-Vice-Chancellor for Research

Professor Lynn Gladden is one of the University's five Pro-Vice-Chancellors, whose role is to take forward strategy and policy development and to support the Vice-Chancellor in providing institutional leadership for the University, particularly in their areas of responsibility. The Pro-Vice-Chancellors work closely with the Heads of Schools and senior professional administrators. As Pro-Vice-Chancellor for Research, Professor Gladden succeeds Professor Ian Leslie.

Professor Gladden CBE, FRS, FREng is the Shell Professor of Chemical Engineering, and Head of the Department of Chemical Engineering and Biotechnology. She is also a member of the Council of the Engineering and Physical Sciences Research Council (EPSRC). Professor Gladden was awarded a CBE in the Queen's Birthday Honours list in June 2009 for services to chemical engineering, having been awarded an OBE in 2001 for services to chemistry. Her particular research interests are in applying magnetic resonance imaging techniques in the fields of heterogeneous catalysis and multi-phase transport in porous media.

Evidence of the first modern humans in North Africa

Excavation of the deepest archaeological trench in North Africa half a century after it was first dug is offering a glimpse of up to 200,000 years of human history.

In 1948, Cambridge academic Professor Charles McBurney stumbled upon a large cave on the north coast of Libya. Returning to excavate it three years later, he sank a trench 14 metres into the floor of the cave, finding layer upon layer of evidence of human occupation going back thousands of years into deep prehistory.

Over 50 years later, excavation resumed in 2007 when Professor Graeme Barker, Director of Cambridge's McDonald Institute for Archaeological Research, led an expedition of 30 academics from 10 research institutes back to the Haua Fteah Cave. Now, mid-way through this five-year project, the researchers have made a fascinating discovery that sheds new light on when modern humans first arrived on Africa's northern shores.

'McBurney's work was a seminal contribution to world prehistory. With techniques available to him in the 1950s, he concluded that the trench spanned about 80,000 years of history. He believed the human jaws that he discovered deep down were pre-modern in anatomy and that modern humans (*Homo sapiens*) arrived in North Africa around 40,000 years ago, which is about when they reached Europe,' explained Professor Barker. 'The advent of new technologies has enabled us to re-evaluate this. Already our findings are showing that this site is probably far older than McBurney realised. The jaws are now recognised to belong to *Homo sapiens*, and we now have definite evidence of our species being in North Africa for at least 80,000 not 40,000 years.'

The team has painstakingly emptied the sediment that McBurney used to re-fill the trench, revealing the original walls of the pit. They have now reached a depth of 10 metres, just below where the jaws were discovered. Using dating technology such as optical stimulated luminescence – which essentially measures the last time a grain of quartz saw the light of day – the researchers have established that they have reached sediment that is 90,000 years old.

PROFESSOR GRAEME BARKER (LEFT) AND ADI INSKEEP (RIGHT)

Excavation of the Haua Fteah Cave, Libya, today (left) and by Charles McBurney in the 1950s (right)

'Now that we have the first definite evidence for our species being in North Africa at least 80,000 years ago, the question is whether they were behaving in ways we would recognise as modern. We are looking for evidence of their technologies and hunting practices and their level of cognition,' explained Professor Barker. 'And since we have another 6 metres to go before we hit bedrock, the deepest archaeological trench in North Africa has potentially a 200,000-year-old story to tell.'

For more information, please contact Professor Graeme Barker (gb314@cam.ac.uk), the Disney Professor of Archaeology. This research was principally funded by the European Research Council, with supplementary funding from the Society of Libyan Studies, the project's sponsor.

Investing in the future of maths

A new Centre for Doctoral Training (CDT) in mathematical sciences will train the next generation of mathematical analysts.

The Engineering and Physical Sciences Research Council (EPSRC) has announced the investment of £13 million to fund three new CDTs at the Universities of Cambridge, Lancaster and Warwick. The new Centres will open at the beginning of the next academic year and will each train at least 40 students over seven years. Each PhD student will develop an original research project and receive a formal programme of taught coursework to broaden their skills and enhance their technical and interdisciplinary knowledge.

The Cambridge Centre for Analysis will be directed by Professors Arieh Iserles and James Norris. It will aim to build up core expertise in mathematical analysis within a cohort of some of the best young mathematical minds in the world. Training will cover the full range of modern techniques of analysis for mathematical modelling, spanning pure, stochastic, computational and applied analysis.

The Centre will provide opportunities for fundamental research, team-based problem solving, industrial secondments and interdisciplinary collaboration. It will create a generation of independent-minded mathematical researchers who will contribute to the long-term scientific, technological and economic well-being of the UK.

For more information, please visit www.maths.cam.ac.uk/cca/

Earthquake research reaches across Europe

Real-time transnational access will enable researchers to participate in experiments all over Europe without leaving the lab.

DR GOPAL MADABHUSHI

Centrifuge at the Department of Engineering's Schofield Centre

In an underground chamber at the 'remotest part' of the University lies the UK's largest centrifuge and the world's most productive machine for observing and measuring geotechnical phenomena. Located at High Cross on Madingley Road, the Turner centrifuge at the Department of Engineering's Schofield Centre travels at speeds of 200 miles per hour and creates 150 times the earth's gravity. The 10 metre diameter centrifuge is being used to model loads and pressures experienced during earthquakes, and to simulate tunnels and wind farms.

Now, thanks to funding from the European Commission (EC), experiments carried out in Cambridge will soon be 'talking' to experiments happening at the same time at sites across Europe. Data will be fed in real-time across the internet to other sites participating in the project, allowing multiple institutions to take part in a common experiment. In all, 23 institutions, each with its own specialist equipment, are involved in research aimed at answering questions about the behaviour of shallow building foundations in earthquakes.

The Seismic Engineering Research Infrastructures for European Synergies (SERIES) project is being coordinated by Dr Gopal Madabhushi and Dr Stuart Haigh. 'European seismic engineering research has tended to suffer from extreme fragmentation of research infrastructures and limited access to equipment between countries,' explained Dr Madabhushi. 'SERIES answers this need by enabling the key actors in Europe's seismic engineering research, including three industrial beneficiaries, to coordinate remote research activities in real-time.'

The project builds on the success of a smaller-scale initiative between the UK's three leading earthquake engineering laboratories at the Universities of Cambridge, Oxford and Bristol with funding from the Engineering and Physical Sciences Research Council (EPSRC). This showed the benefits of creating real-time, grid-based communications to provide access to experimental facilities and data.

For SERIES, the efficiency and cost-effectiveness of resource usage is considerable: it's been estimated that the annual cost to the EC of the four-year programme is less than 1.35% of the total present value (€190 million) of the material resources to be shared by the 23 participants.

For more information, please contact Dr Gopal Madabhushi (mspg1@eng.cam.ac.uk) or visit the SERIES website (www.series.upatras.gr/).

Cambridge wins Grand Prize for iGEM 2009

A team of Cambridge students has been awarded the Grand Prize for their entry into an international synthetic biology competition.

Against stiff competition from over 100 teams in top international institutions, the Cambridge team was awarded the Grand Prize at the 2009 International Genetically Engineered Machine (iGEM) competition finals at the Massachusetts Institute of Technology (MIT) in November. As well as winning the overall prize for best project and the BioBrick Trophy, the team was awarded a gold medal and trophy for the Best Environment Project.

The undergraduate students (Vivian Mullin, Alan Walbridge, Shuna Gould, Siming Ma, Mike Davies, Megan Stanley and Crispian Wilson) faced the challenge of conceiving, designing and implementing a synthetic biological system using standard, interchangeable DNA parts ('BioBricks') and operating it in living cells.

Their winning idea, 'E.Chromi', is based on the engineering of bacteria that are normally found in the gut, in order to generate multicoloured pigments and provide improved biosensors. One hypothetical application of the invention was explored with Daisy Ginsberg and James King from the Royal College of Art: the engineered bacteria could be ingested as a probiotic to provide cheap, personalised disease monitoring. Chemical changes in the gastrointestinal tract caused by disease would result in a colour signal in faeces that is bright enough to be visible to the human eye.

The team was supported throughout the project by faculty staff from the Departments of Plant Sciences, Genetics, Pathology, Engineering, and Chemical Engineering and Biotechnology. One of the advisors, Dr Jim Haseloff from the Department of Plant Sciences, described the special role that the competition has played in Cambridge: 'Since 2005, when Cambridge was the first UK team to take part in iGEM, the competition has brought together a network of researchers interested in the interplay of biology and engineering, helping to strengthen the emerging field of synthetic biology in Cambridge. The competition is a highly motivating and educational experience for all concerned and we're delighted that the innovative ideas of this year's team have been so well received by the judges.'

For more information, please visit www.synbio.org.uk/igem.html and www.echromi.com/

New Regius Professor of Botany

Cambridge has a new Regius Professor, after Her Majesty the Queen conferred the royal title on the University's existing Professorship of Botany.

Cambridge's Regius Professors: back row, from left, Sir David Baulcombe, Botany; Richard Hunter, Greek; David Ford, Divinity; David Ibbetson, Civil Law; front row, from left, Robert Gordon, Hebrew; Richard Evans, Modern History; Patrick Sissons, Physic

The new Regius Professorship of Botany brings the number of Regius Professors at Cambridge to seven, joining Civil Law, Divinity, Greek, Hebrew and Physic (all founded by Henry VIII in 1540) and Modern History (founded by George I in 1724). Historically, Regius Professorships were created by the Crown in disciplines judged to be fundamental, and for which there is a continuing and significant need. The new position links the University's 800th Anniversary celebrations with the Darwin Anniversary in 2009 as J.S. Henslow, Charles Darwin's mentor, was Professor of Botany at Cambridge.

Sir David Baulcombe is the first to hold the new Regius Professorship of Botany. He was knighted in the 2009 Queen's Birthday Honours list for services to plant science, and in 2008 was awarded the Albert Lasker Basic Medical Research award for his discovery of how small molecules of ribonucleic acid (RNA) govern gene activity through a process known as RNA silencing. Professor Baulcombe's research has unravelled how this mechanism is important in gene regulation and as a natural weapon in mechanisms of disease resistance and defence against viruses in plants.

For more information about the Department of Plant Sciences and Professor David Baulcombe's research, please visit www.plantsci.cam.ac.uk/research/

New blood test for schizophrenia

The first objective means of diagnosing a disorder that affects over 24 million people worldwide has been discovered.

Finding an effective early way to diagnose schizophrenia has been a long-term dream of Dr Sabine Bahn at the Cambridge Centre for Neuropsychiatric Research, located in the Department of Chemical Engineering and Biotechnology. For the past 13 years, Dr Bahn and her team have been progressing towards a greater understanding of the molecular processes that lead to the disorder. To develop the research, Dr Bahn founded Psynova Neurotech Ltd in 2005 with initial Cambridge Enterprise Proof of Concept funding, followed later by an investment from the Cambridge Enterprise Seed Funds.

Now, an objective blood test for the diagnosis of schizophrenia is due to be launched in 2010. This follows a collaboration between Psynova and Rules-Based Medicine Inc. (RBM) which recently led to the discovery and characterisation of a combination of protein biomarkers that can be used as an adjunctive aid in the differential diagnosis of schizophrenia. On achieving this milestone, Texas-based RBM announced additional investments in Psynova and now has a controlling interest in the company.

Dr Sabine Bahn (far right) and two member of her team

'While several psychiatric conditions share symptoms, the clinical interventions vary, making it important to establish an accurate diagnosis as early as possible,' explained Dr Bahn. 'We intend to develop a minimally invasive, objective test to aid the early diagnosis of schizophrenia and differentiation from bipolar disorder and major depression.'

Head of Seed Funds at Cambridge Enterprise Dr Geraldine Rodgers added: 'Schizophrenia is a tough condition to diagnose and this discovery has the potential to make a difference to those who suffer from this incapacitating disease.' The two companies are working with leading psychiatric researchers to gain additional clinical input to maximise the benefit for patients and the healthcare system.

For more information, please contact Cambridge Enterprise Ltd (Tel: +44 (0)1223 760339; email: enquires@enterprise.cam.ac.uk) or visit www.enterprise.cam.ac.uk/

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Strategic research partnership drives materials science research and training

Rolls-Royce and the Engineering and Physical Sciences Research Council (EPSRC) will work jointly with the Universities of Cambridge, Birmingham and Swansea in a new £50 million strategic partnership.

Over the next 10 years, a Strategic Partnership in Structural Metallic Systems for Advanced Gas Turbine Applications will develop materials skills and knowledge to support the development of future gas turbines. It builds on a highly successful University Technology Partnership funded by Rolls-Royce between the Universities of Cambridge, Birmingham and Swansea.

Fundamental materials research is needed to develop materials that will improve the efficiency and environmental sustainability of gas turbines, which provide the power for many applications including aircraft, ships and electricity generation. Principal Investigator Dr Howard Stone, from the Department of Materials Science and Metallurgy, explained: 'Dwindling resources and climate change are forcing engineering designers to utilise materials and energy supplies with ever-greater efficiency. One approach is to find materials that withstand gas combusting at higher temperatures, since this uses less energy and creates less CO_2.'

To meet this challenge, the programme brings together a critical mass of researchers to increase the efficiency of known materials or to find new materials that can be used for the hottest parts of the engine. Cambridge's contribution will be to develop and test new structural metallic materials that will withstand ever more extreme conditions of temperature and pressure, as well as being safe and economical.

The funding also includes a Doctoral Training Partnership (DTP) to help create the next generation of world-class materials scientists and metallurgical engineers. 'The UK is experiencing a chronic shortage of materials scientists despite a clear industrial need,' said

ROLLS-ROYCE

Dr Cathie Rae, who is coordinating the Cambridge DTP. A total of 60 students across the three universities will undertake research of strategic value to Rolls-Royce and the gas turbine industry in general, as well as taught courses amounting to a year of training. 'Our goal is to equip scientists of the future with the skills needed to underpin industries as diverse as aeroengineering, nuclear power and construction.'

For more information, please contact Dr Howard Stone (hjs1002@cam.ac.uk) or Dr Cathie Rae (cr18@cam.ac.uk).

Naked Scientist takes on materials science

The Rolls-Royce Strategic Partnership includes funds to recruit a new member to the award-winning Naked Scientists team, whose weekly radio programmes and podcasts reach a worldwide audience of more than 20 million people per week. Working with Naked Scientist Dr Chris Smith, the new team member's focus will be to publicise materials science research as a means to improving the general perception of metallurgical engineering and to encourage more young people into science and engineering.

For more information, please contact Dr Chris Smith (cs222@cam.ac.uk) or visit www.thenakedscientists.com/

Unlocking the history of the book

A new chapter in textual scholarship is beginning, thanks to the launch of the Centre for Material Texts.

Books and manuscripts of any period can have unique and complicated personal histories. 'From the moment of inception, a text becomes a material object that can be subjected to a whole host of life events, which might encompass how it is copied, edited, published, disseminated, reviewed, revised or preserved,' explained Dr Jason Scott-Warren, Director of the new Centre for Material Texts in the Faculty of English. 'Whether the text is a medieval manuscript copied by monks, a commonplace book passed from one owner to another, or a bestseller converted into a screenplay, each has an embodied history.'

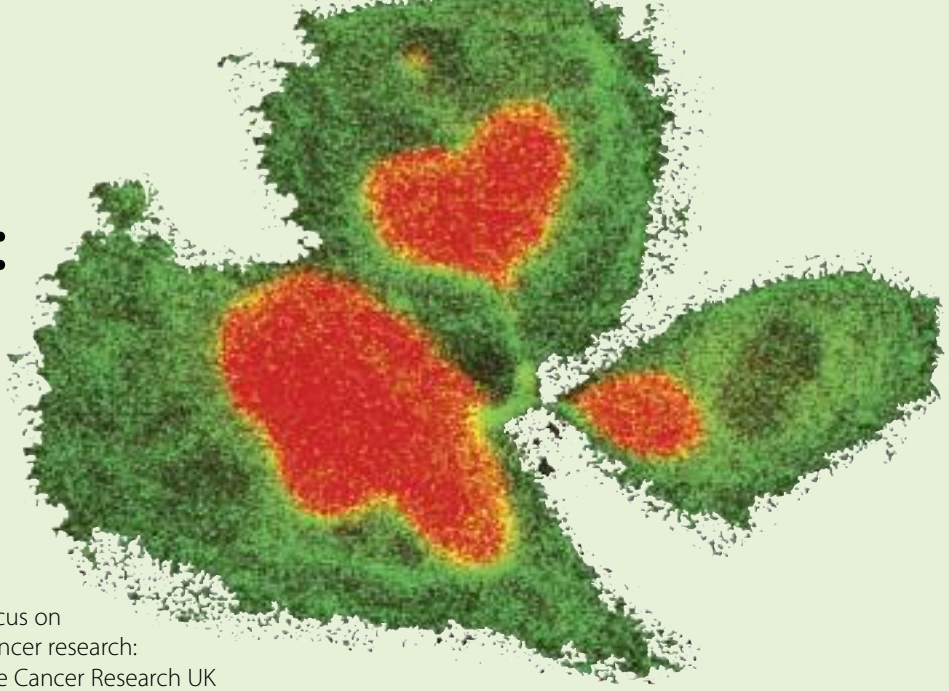
The recently launched Centre will foster teaching and research in the study of material texts across Cambridge. It will offer intellectual and practical support, as well as opportunities for collaboration through sharing of ideas and expertise. 'Our aspiration is to draw in researchers working in different disciplines, different historical periods and different manifestations of text,' said Dr Scott-Warren.

One aim of the Centre will be to coordinate web custodianship of digitisation projects such as the recently completed Scriptorium project (see page 26), which provides rich and varied resources for manuscript research and teaching.

'The Faculty has a strong track record in bibliographical scholarship, manuscript studies and textual research of various kinds,' explained Professor Adrian Poole, Head of the Faculty of English. 'The Centre will help us to coordinate and enhance this research, and to reach out to other disciplines, united by a common fascination with the materiality of the sources we work with.'

For more information, please contact Dr Jason Scott-Warren (jes1003@cam.ac.uk).

Cambridge Cancer Centre: the vision



Professor Sir Bruce Ponder describes the vision of a Cambridge-wide initiative to link world-class cancer research to improved patient care.

Cancer will affect one in three of us during our lifetime and is a leading cause of death and disability worldwide. Today though, there is a new sense of optimism, as scientific advances have led us to the point where an understanding of the molecular and cellular biology of cancer is being translated into real benefits for patients.

Over the past 10 years, cancer research efforts within the University, the Cambridge University Hospitals NHS Foundation Trust (Addenbrooke's) and the many institutes and centres in Cambridge and nearby have been drawing science and medicine closer together. Helping to connect this research community, a virtual Cambridge Cancer Centre was launched in 2006 to promote interactions among researchers and clinicians working in diverse areas, as well as with biotech and pharmaceutical companies. The virtual organisation promotes information exchange between members, hosts cross-disciplinary scientific meetings (see page 35) and makes available pump-priming grants for new collaborative research with potential clinical application.

Creating the research environment

Clinical research must be nourished and renewed from fundamental research. Across the University, cancer research is strongly represented in many departments – from the biomedical sciences to the physical sciences, and increasingly embracing mathematics, engineering and computational biology. Research projects are investigating all aspects of cancer, whether it's at the level of DNA, cells or populations. Research goals include identifying new therapeutics, imaging tumours, and devising computational approaches that analyse vast amounts of data.

Three major laboratories in Cambridge have been created with a focus on cancer research: the Cancer Research UK Cambridge Research Institute (CRI)/Li Ka Shing Centre, the Hutchison/Medical Research Council Research Centre, and part of the Strangeways Research Laboratory. Together, they provide space for almost 500 researchers, plus state-of-the-art supporting facilities for technologies such as genome sequencing, molecular imaging, microscopy and computational biology. But more than this, the new laboratories are bridging the interface between science and the clinic.

Translating research into patient care

Successfully applying the results of research requires an excellent clinical service and clinical research environment. Cambridge is very much a cancer centre when it comes to strengths in clinical and healthcare innovation. Cancer was one of three main themes when Cambridge University Health Partners, which includes the Cambridge University Hospitals NHS Foundation Trust and the University, was selected last year by the Department of Health as one of five Academic Health Science Centres in the UK. It was also the leading theme when an international panel selected Cambridge as one of five Biomedical Research Centres funded by the NHS in 2006.

Intensive studies in experimental medicine are being built up in collaboration with major pharmaceutical companies and academic researchers. Multidisciplinary clinical teams for each cancer type have been created that include University and NHS staff working closely together, enabling research and clinical care to proceed side by side.

Catalysing great ideas

New ideas are likely to lie at the boundaries between disciplines or between laboratory and clinic, and even at the margins of conventional career paths and funding. At the CRI, for example, many researchers are also clinicians, and oncologists work alongside mathematicians, biochemists and cell biologists. Across Cambridge, an important part of the long-term vision is to stimulate training programmes to equip researchers to cross traditional academic boundaries.

Playing to scientific strengths, much current research is focusing on achieving earlier diagnosis and treatment in high-risk groups, discovering the determinants of treatment resistance, and providing individually tailored treatment (personalised medicine) based on genomic information. By harnessing the catalytic effect of the Cancer Centre on Cambridge science, great opportunities lie ahead in the development of powerful new approaches to diagnosing and treating cancer.

Professor Sir Bruce Ponder

For more information, please contact Professor Sir Bruce Ponder (bruce.ponder@cancer.org.uk), the Li Ka Shing Professor of Oncology, Director of the Cancer Research UK CRI/Li Ka Shing Centre (www.cambridgecancer.org.uk/) and Director of the Cambridge Cancer Centre (www.cancer.cam.ac.uk/).

Beacons of life and death: chromatin and cancer

A new generation of cancer therapeutics is on the horizon thanks to fresh light being shed on how genes are switched on and off.

HENNING DALHOFF/BONNIER PUBLICATIONS/SCIENCE PHOTO LIBRARY

DNA is coiled around histone proteins (shown here as blue beads) and supercoiled into fibres of chromatin before being condensed into chromosome structures

The basic functioning of our cells is governed by complex signalling pathways that relay what's happening around and within cells to their control centre – the cell's nucleus. The nucleus responds by regulating which genes in our DNA are switched on and off. When this fine-tuned regulation goes wrong, diseases such as cancer can result.

At the heart of this gene regulation are proteins called histones, around which DNA is wrapped rather like beads on a string, before being supercoiled into a structure called chromatin. But histones are not just a packing material. Histones also act as beacons, guiding enzymes to specific locations on the genome in order to turn genes on and off. Professor Tony Kouzarides' research group at the Wellcome Trust/Cancer Research UK Gurdon Institute discovered in the 1990s that this process is governed by enzymatic machinery that modifies the histone proteins. Many of the pathways that lead to the modification of histones are deregulated in cancer.

Professor Kouzarides' latest discovery, in collaboration with Professor Tony Green's group in the Department of Haematology, has made a crucial link between a faulty histone-modifying enzyme and leukaemia.

New route to leukaemia

The research, funded by Cancer Research UK and published recently in *Nature,* was carried out by Dr Andy Bannister and PhD student Mark Dawson. They studied an enzyme known as Janus kinase 2 (JAK2), which functions as a signal transducer – essentially, a component of the cell's signalling pathways that converts one type of signal to another. Faulty JAK2 has been linked with leukaemia for a number of years.

The breakthrough came when the scientists found an unknown signalling function of JAK2. Previously, JAK2 had been thought to transduce signals only within the main part of the cell, but the researchers showed that it can enter the nucleus and modify histones. Importantly, they discovered that the modification normally switches on a gene that causes leukaemia, and makes it remain on constantly. The researchers had uncovered a direct mechanistic link between a signal transducer, histone modification and cancer.

Towards therapeutics

The goal now is to continue their ongoing search for other enzymes that modify histone proteins (the group has discovered several already). Professor Kouzarides believes that these hold the key to a future generation of cancer therapeutics. A University spin-out, Chroma Therapeutics, was launched in 2001 to exploit his research and that of others in the chromatin field, with the aim of harnessing the new understanding of chromatin biology to develop novel therapeutics to prevent, diagnose and treat cancer.

Leaps in understanding the basic molecular genetics that control and disrupt cell function are bringing a new generation of therapeutics closer. Just as histone proteins act as beacons for drawing signalling enzymes towards DNA, they are also beacons for cancer researchers intent on increasing the arsenal of anticancer therapeutics.

Professor Tony Kouzarides

For more information, please contact Professor Tony Kouzarides (t.kouzarides@gurdon.cam.ac.uk), the Royal Society Napier Professor, at the Wellcome Trust/Cancer Research UK Gurdon Institute (www.gurdon.cam.ac.uk/). This research was published in *Nature* (2009), 461, 819–822.

Professor Kouzarides has recently founded 'Vencer el Cancer' (Conquer Cancer), a cancer charity in Spain whose goal is to raise funds from the public to fund cancer research and drug discovery. The idea is to emulate Cancer Research UK in the fundraising strategies that have been so successful in the UK.

Scientists at Strangeways Research Laboratory are leading the search for the 'genetic cards' that determine an individual's risk of cancer.

Cancer: what's on the cards?

How likely we are to develop cancer is determined by our genes and our lifestyle. Likening this to a hand of cards, the risk of cancer depends on whether we inherit good cards or bad cards and also how we play them (our lifestyle). Some genes carry a very high risk, which is why some individuals have a particularly strong family history of cancer. Most of the time, however, cancer risk is determined by a combination of genes conferring a more moderate risk; nevertheless, the overall risk can be high (a bad hand) if there are enough of these genes.

At Strangeways Research Laboratory (SRL) in Cambridge, the research groups of Professor Doug Easton, Dr Paul Pharoah and Dr Alison Dunning, supported with over £9 million of funding from Cancer Research UK, are working out the role of normal human genetic variation in cancer risk – essentially, which hands of cards are worse than others.

The SEARCH begins

Several high-risk gene defects, such as mutations in BRCA1 and BRCA2 in breast cancer, have been identified through family studies. Work in the 1990s at SRL by Professor Sir Bruce Ponder, who is now Director of the Cancer Research UK Cambridge Research Institute (CRI), and Professor Easton helped track down these two genes. However, among the general population, these defects are usually rare, and most cancers are the result of inheriting several more-common gene mutations. For breast cancer, these more-common gene defects account for as much as 80% of inherited risk, according to findings at SRL.

'The trouble is, the individual effects of common genetic variants are small and to get reliable evidence about specific variants you need to sample large numbers of people,' explained Professor Easton, Director of the Cancer Research UK Genetic Epidemiology Group. Key to finding these mutations has been the assembly at SRL of one of the largest population studies of cancer ever conducted, along with the unique expertise that the team has gathered together in cancer epidemiology, biostatistics, large-scale genetic analysis and public health medicine.

This work was started in 1996 by Professor Ponder and Professor Nicholas Day, who recruited Dr Paul Pharoah as a Clinical Fellow to enrol patients with breast cancer. The enrolment was later extended to include patients with ovarian, colorectal or uterine cancer, as well as participants with no history of cancer. The project, now called SEARCH, was further extended five years ago to include bladder, brain, kidney, oesophageal and pancreatic cancers, as well as melanoma and non-Hodgkin's lymphoma. 'Our early investment in well-curated and very large study sets, with blood samples, pathology review and clinical data, has been absolutely crucial as it has provided the statistical power for reliable conclusions about common genetic variants,' explained Professor Ponder. Today, SEARCH numbers nearly 27,000 cases and normal controls from the East Anglia region, providing a remarkable and growing resource: by 2013, the hope is that this will have expanded to 35,000.

BCAC: Breast Cancer Association Consortium

BOADICEA: Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm

CIMBA: Consortium of Investigators of Modifiers of BRCA1/2

EMBRACE: Epidemiological Study of Familial Breast Cancer

OCAC: Ovarian Cancer Association Consortium

PRACTICAL: Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome

ProtecT: Prostate Testing for Cancer and Treatment

SEARCH: Studies of Epidemiology and Risk Factors in Cancer Heredity

Going global

'SEARCH has shown that the size of the dataset is really important for assessing the impact of common genetic variants accurately,' explained Dr Pharoah, who leads a research group at SRL from the Department of Oncology. 'The logical next step was to combine data from SEARCH with other studies that had been happening worldwide.'

Cambridge now coordinates five international consortia of study groups: two consortia studying breast cancer, one each studying ovarian and prostate cancers, and a newly formed consortium to examine genetic differences underlying adverse side-effects from cancer radiotherapy (see right panel). From SRL, the consortia pull in not just SEARCH but also other studies such as ProtecT, a prostate cancer study led by Cambridge's Professor of Surgical Oncology, David Neal, together with Professor Freddie Hamdy in Oxford and Professor Jenny Donovan in Bristol; and the familial breast cancer study EMBRACE, led by Professor Easton. The scale of the endeavour is unprecedented in population studies, and the European Union has recently awarded €12 million to coordinate these large-scale genetic studies in breast, ovarian and prostate cancers.

'Apart from increasing the reliability of the data,' said Professor Easton, 'the international consortia afford the opportunity to study populations from different parts of the world where different genetic and lifestyle factors are operating.'

Gene hunting

Improvements in technology that would have been hard to imagine when SEARCH began are now being used to analyse the data, demonstrating the enormous foresight in setting up such a resource a decade ago.

'We know that there are about 10 million variants in the genome, but choosing the right ones to test for association with cancer has in the past owed a great deal to chance, with the result that very few positive associations were identified,' said Dr Dunning, who leads the high-throughput laboratory team within the SRL. 'Now, though, thanks both to the ability to carry out genome-wide scans and the samples collected through the international consortia, we can pinpoint the variants that are definitively linked to the risk of cancer.'

A full genome scan for breast cancer, the first of its kind, was completed in 2007 by the researchers and published in *Nature*. Full genome scans of prostate and ovarian cancers have since followed in *Nature Genetics*. In the latest scan, published in October 2009, the genomes of 38,000 men with and without prostate cancer were analysed for over 43,000 single differences in DNA (called single nucleotide polymorphisms or SNPs), revealing multiple new cancer gene regions.

To date, 13 predisposing gene regions have been identified for breast cancer, five for ovarian cancer and 27 for prostate cancer, findings that have significant implications for targeted screening and prevention in the future. Since most of these newly discovered regions contain genes that had not previously been considered in cancer, they will also provide new insights into the biology of the disease. Going forward, Professor Ponder's group at the CRI is developing phenotypic assays as a read-out of cancer risk, studying how risk genes exert their function and searching for molecular markers for future studies of early diagnosis and prevention. Professor Fiona Watt at the Wellcome Trust Centre for Stem Cell Research is also studying the biological effects caused by these gene defects to understand what goes wrong in cancer.

Professor Neal, in the Department of Oncology and CRI, has been investigating whether a protein made by one of the newly discovered prostate loci can be used as a screening and diagnostic marker in prostate cancer since it can be measured in serum and urine. Early results suggest not only loss of the protein in prostate cancer, but also a decrease in men who possess the high-risk form of the gene but who have not yet developed prostate cancer.

Translational tools

But what does this all mean to understanding our own risk? For breast and ovarian cancer, Dr Antonis Antoniou and Professor Easton have developed a computer model named BOADICEA that can predict an individual's risk of these cancers. The tool is already being used by genetic counsellors to identify high-risk individuals, referring them for counselling and regular screening if appropriate, and providing advice about ways to lower their risk. As new data come to light from the genome scans, BOADICEA will continually be improved, providing increasingly accurate information to individuals wishing to know the hand of genetic cards that they've been dealt.

Worldwide consortia led by Strangeways Research Laboratory

BCAC: 100,000 breast cancer cases and controls; 55 study groups

CIMBA: 25,000 breast cancer cases and controls; 42 study groups

OCAC: 30,000 ovarian cancer cases and controls; 34 study groups

PRACTICAL: 25,000 prostate cancer cases and controls; 27 study groups

Radiogenomics Consortium: newly formed; 23 study groups

Dr Alison Dunning, Professor Doug Easton and Dr Paul Pharoah (left to right)

For more information, please contact Professor Doug Easton (doug.easton@srl.cam.ac.uk), Dr Paul Pharoah (paul.pharoah@srl.cam.ac.uk) and Dr Alison Dunning (alisond@srl.cam.ac.uk) at the Strangeways Research Laboratory (www.srl.cam.ac.uk/) or visit the SEARCH website (www.srl.cam.ac.uk/search/Homepage.htm).

DR KIM JENSEN, WT CENTRE FOR STEM CELL RESEARCH

Cambridge scientists are asking what role stem cells play in how cancer develops, spreads and relapses.

Understanding how cancer cells grow

Stem cells (shown here in red) are responsible for the maintenance and regeneration of all the cells in a tissue

Most tissues in the human body are maintained by stem cells – master builders and repairers that replenish different types of cells when needed. The unique properties of stem cells are of great interest to scientists investigating the possibility of regenerating and repairing human tissues. But stem cells have also come under close scrutiny in relation to cancer, since the ability to self-renew is a characteristic of tumours. Research into cancer stem cells is offering new insight into how cancer cells grow and how some tumours relapse even following powerful therapy.

Cambridge has a very active stem cell community, recognised as a centre of excellence by the Wellcome Trust (WT) and the Medical Research Council (MRC). A major research theme within this community is the Cancer Stem Cell Programme at the MRC Centre for Stem Cell Biology and Regenerative Medicine. Professor Fiona Watt, who directs the Programme, explained why cancer stem cells are so interesting: 'Pathologists have known for centuries that within a single tumour there can be cells that differ in maturity. It is now becoming clear that this heterogeneity reflects, at least in part, the existence of cancer stem cells and their offspring, and that these cells play a crucial role in the life history of cancer. Eradicating these master builders would strike at the heart of the tumour.'

Cancer stem cells

The Cancer Stem Cell Programme brings together clinicians and scientists with expertise in haematological, epithelial and brain cancers.

One of the best-studied adult stem cell systems is the process by which the many different cell types found in blood are constantly replenished. Professor Tony Green and Dr Brian Huntly in the Department of Haematology are using this process as a paradigm for understanding leukaemias: 'We are especially interested in the molecular rewiring that underlies the change from a normal cell to a cancerous stem cell,' explained Professor Green. A recent success has been the discovery of a new molecular mechanism for leukaemia (see page 9).

To identify cancer stem cells and their complex interactions, researchers frequently develop biological models of cancer. Dr Stephen Goldie in Professor Watt's lab, in collaboration with clinicians at Cambridge University Hospitals NHS Foundation Trust, is investigating cancer stem cells in human head and neck tumours by creating models that recapitulate the original human tumour. 'Interactions between the tumour and its environment are being tracked by state-of-the-art imaging technology to establish which cells are responsible for making the tumours and what can be done to make the tumour shrink and stop spreading,' explained Dr Goldie.

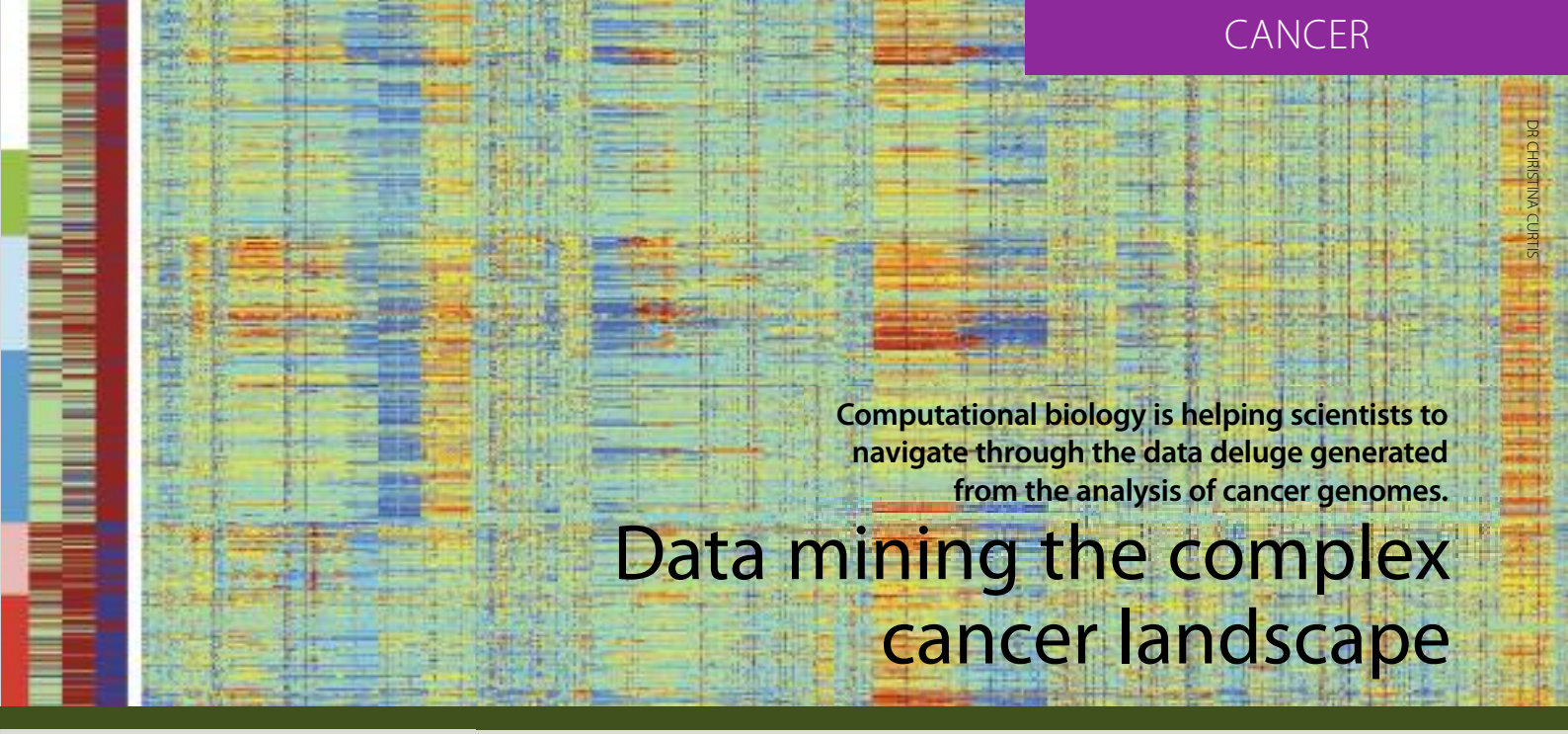
Scientists from the Centre for Brain Repair in the Department of Clinical Neurosciences and the WT Centre for Stem Cell Research are investigating stem cells in brain cancer. 'Brain cancer accounts for a disproportionate number of cancer deaths and new treatments are urgently required,' explained Dr Colin Watts, Consultant Neurosurgeon, from the Centre for Brain Repair. 'These tumours contain stem-like cells that are resistant to current treatments. Work in the Centre aims to understand the mechanisms underlying this resistance and to develop ways of killing these cells.'

Driving new treatments

The current thinking is that cancer stem cells constitute a minority of the cells within a tumour and, although they are capable of dividing continually, they may do so relatively slowly. Most therapies are targeted towards rapidly dividing cells, which might kill the bulk of the tumour but not the cancer stem cells. Understanding more about cancer stem cells is therefore crucial, as Professor Watt explained: 'Future treatments that are specific for cancer stem cells will not only be more effective in treating the disease, but will also incur less collateral damage to the patient's normal tissues.'

Professor Fiona Watt

For more information, please contact Professor Fiona Watt (fiona.watt@cancer.org.uk), the Herchel Smith Professor of Medical Genetics, at the WT Centre for Stem Cell Research (www.cscr.cam.ac.uk/) and the Cancer Research UK Cambridge Research Institute/ Li Ka Shing Centre (www.cambridgecancer.org.uk/).



DR CHRISTINA CURTIS

Computational biology is helping scientists to navigate through the data deluge generated from the analysis of cancer genomes.

Data mining the complex cancer landscape

Searching for patterns in cancer genomes amid vast amounts of information

The advent of new technologies has enabled researchers to interrogate human genomes at unprecedented resolution. These technologies have led to a wealth of genomic information that has the capacity to shed new light on complex diseases, but they also generate far too much data to interpret by eye. Consequently, novel computational and statistical techniques have evolved to extract meaningful patterns from the data ('data mining') and to integrate this with other types of biological information in an attempt to make sense of what it all means.

In Cambridge, a collaboration between the Computational Biology group at the Cancer Research UK Cambridge Research Institute (CRI), led by Professor Simon Tavaré (also at the Department of Applied Mathematics and Theoretical Physics), and Professor Carlos Caldas and Dr James Brenton (who are both at the CRI and the Department of Oncology) seeks to do just this, demonstrating the power of combining expertise in statistics, computational and experimental biology, and clinical medicine to understand cancer.

METABRIC

Breast cancer, like other malignancies, is driven by the progressive acquisition of key genetic alterations that confer growth advantages on the cell. Most of the acquired aberrations are merely 'passenger' events that do not influence cancer progression, whereas the 'driver' events are critical mediators of disease. It is these 'driver' events and the effects they elicit that researchers seek to identify, the problem being akin to searching for a needle in a haystack.

METABRIC (Molecular Taxonomy of Breast Cancer International Consortium) is an Anglo-Canadian effort aimed at finding the 'needles', and is funded by Cancer Research UK and the British Columbia Cancer Foundation. Given the substantial molecular heterogeneity among breast cancer patients, METABRIC seeks to interrogate the genomic and transcriptional landscape of over 2,000 clinically annotated breast tumour specimens to generate a robust molecular description of the disease.

Each sample is examined for differences in gene expression levels, as well as for alterations in the number of copies of each gene, by combining measurements from nearly two million probes that query the genome at sequential positions. Add to this a variety of other data types and five years of clinical history, and you wonder how the sheer volume of data can be processed, let alone interpreted. In fact, a major challenge with such high-dimensional datasets is the identification of true differences amid inherent background noise. How can one see the forest for the trees in the cancer genome landscape?

Seeing the forest for the trees

Dr Christina Curtis in the Computational Biology group is leading the analysis of massively parallel technologies using computational and statistical methods to make sense of this vast data deluge. Much of her research relies on high-performance computing to process these and other large datasets. Fortunately, the CRI houses a computer cluster with nearly 500 cores and multiple high-memory nodes that will expand to meet the growing need for computational capacity.

Using novel analytical approaches for data integration and mining, Dr Curtis and her team have defined additional subtypes of breast cancer based on their unique molecular characteristics, providing fresh insight into mechanisms of breast cancer tumourigenesis. Future work will relate these molecular profiles to specific clinical phenotypes and identify markers that improve the classification of breast cancer. Importantly, the techniques employed for METABRIC are sufficiently general to be applied to a variety of other cancer datasets.

Computational biology is providing the means to navigate through large-scale, multi-dimensional datasets. In doing so, it can help to build a holistic, systems-level perspective on cancer that will shape future clinical practice.

Professor Simon Tavaré, Dr James Brenton and Professor Carlos Caldas (left to right)

For more information, please contact Professor Simon Tavaré (st321@cam.ac.uk) and Dr Christina Curtis (cc529@cam.ac.uk) at the Cancer Research UK Cambridge Research Institute/Li Ka Shing Centre (www.cambridgecancer.org.uk/).

Which anticancer drugs should be progressed to clinical trials?

Given that it costs an estimated $1 billion to bring a new cancer drug to market, can better decisions be made about which drugs to test in the clinic?

Smart testing for smart drugs

Discovering and evaluating anticancer drugs is a billion dollar business. Much effort is put into the discovery of novel drug targets and then elegant chemistry approaches are used to design and synthesise new therapeutics. 'With the increasing biological understanding of cancer, an increasing repertoire of potential targets has been identified,' explained Professor Duncan Jodrell, at the Cancer Research UK Cambridge Research Institute (CRI). 'But, in the past, time and money have been wasted performing large-scale clinical trials on compounds that end up not having a significant impact on cancer. With many more potential drugs, we need to avoid this happening in the future'. Therefore, a major question is which drugs should be progressed to clinical trials?

Professor Jodrell and Dr David Tuveson, also at the CRI, believe that the answer lies in re-designing the way that preclinical studies are performed and in developing more-relevant animal models of the human disease. Essentially, smart drugs deserve smart evaluation. 'The development of anticancer drugs is therefore likely to have the highest impact when performed at centres that are world-leading in preclinical cancer models, novel therapeutics, molecular imaging and 'science-led' clinical application of novel therapies in patients,' explained Dr Tuveson. 'All of these components are coming together at the CRI and laboratories close by.'

GEMs of discovery

For many years, mouse models have been an invaluable resource to understand the mechanisms that underpin cancer in human patients. These models have become increasingly sophisticated, starting with xenograft models, in which part of a tumour removed from a patient is transplanted into mice, through to the latest genetically modified mouse (GEM) models, which carry the mutations that have been associated with particular human cancers.

'One bottleneck for bringing new therapies into the clinic is the extent to which preclinical testing quickly and accurately predicts how well a drug will perform once it enters clinical trials in patients,' explained Dr Tuveson, who leads the Tumour Modelling and Experimental Medicine group. 'Our goal is to improve the ability to discriminate between drugs that will have significant patient benefits and those that won't.'

Dr Tuveson's particular focus has been on pancreatic cancer and melanoma – two of the most difficult cancers to treat. Despite the fact that we now know which gene is predominantly responsible for each of these types of cancers, patients have a poor prognosis as few treatments are available and many tumours do not respond to them.

Recently, his group discovered a new mechanism that might explain why pancreatic cancer is often resistant to

gemcitabine, a commonly used anticancer treatment. Working with colleagues at Cambridge University Hospitals NHS Foundation Trust (Addenbrooke's) and laboratories in the USA and Europe, the scientists found that resistance to chemotherapy is the result of the pancreatic tumours having a poor network of blood vessels, which makes it harder for drugs to reach the tumour. This result, published a few months ago in *Science*, may also explain why anticancer drugs targeted at blood vessels (which some tumours have in abundance) don't work for pancreatic cancer.

'Working out why some tumours show a disappointing response to chemotherapeutic drugs has enabled us to look at what can be done to overcome this therapeutic intractability,' said Dr Tuveson. 'If the door has been closed to therapy, perhaps we can find a way of reopening it?' Early studies have shown that a compound called IPI-926, created by Infinity Pharmaceuticals, reduces the amount of tissue surrounding the tumour, allowing greater access for gemcitabine.

Dr Tuveson is also working with colleagues at the Wellcome Trust Sanger Institute to identify genes and pathways that influence cancer development – information that will be used to develop new models that mimic human cancers. The proximity in Cambridge of several drug development programmes – such as the Cambridge Molecular Therapeutics Programme at the Hutchison/Medical Research Council (MRC) Research Centre (see page 18) and groups within the Departments of Chemistry and Biochemistry – will offer broad access to novel therapeutic classes for this work.

Entering a new phase

'Although the results are extremely promising,' said Dr Tuveson, 'these are early days and we need to show that this approach is safe to use in humans before we can consider adding the new compound to cancer treatments.' To do this, Dr Tuveson is working with Professor Jodrell, who leads the Cancer Research UK Pharmacology and Drug Development Group at the CRI and a closely associated Early Phase Trials Team based in Addenbrooke's Hospital.

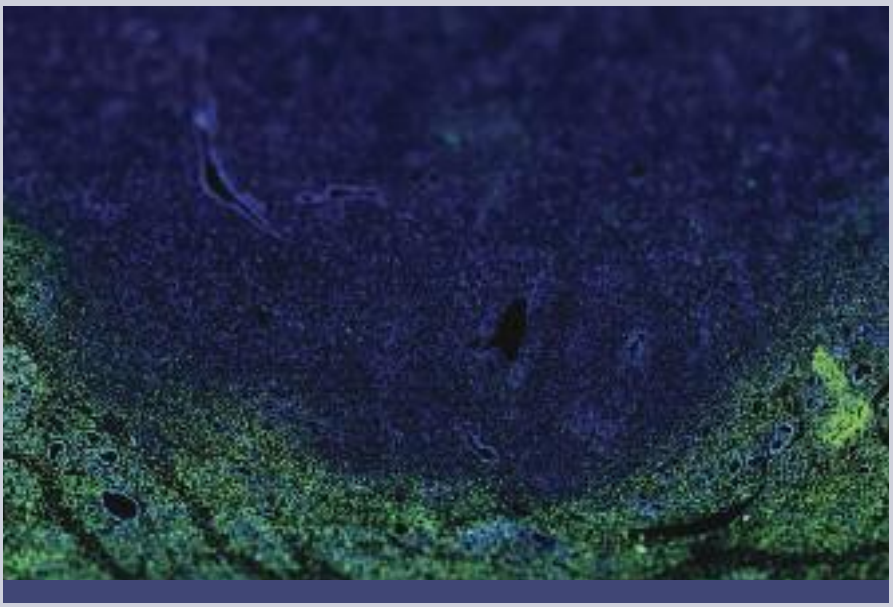
Professor Jodrell is interested in what anticancer drugs do to the body (pharmacodynamics) and how the body handles the drug (pharmacokinetics). 'These are important determinants of successful therapy since the measurements provide information on whether the drug is hitting the right target. We also learn how long the drug hangs around to do this before it's metabolised or eliminated.'

An oncology clinic for pancreatic cancer patients is being developed at Addenbrooke's Hospital and early phase clinical trials are performed in the Wellcome Trust Clinical Research Facility on the same campus. This allows the preclinical studies initiated in CRI laboratories to be translated into clinical benefits for patients. Trials will be available for patients with both early and advanced disease. 'We will be looking for biomarkers that can identify which tumours will respond to a particular treatment, as well as markers that demonstrate early that the treatment is working,' explained Professor Jodrell. 'The goal is to identify which patients will benefit from drugs, and to get more information at an earlier stage to inform those 'go/no go' decisions for progressing a drug through to later-phase clinical trials.' For both the preclinical and clinical studies, novel imaging techniques devised by Professor Kevin Brindle (see page 16) and Professor John Griffiths at the CRI may provide instantaneous assessment of response to treatment. In patients, these non-invasive imaging tools will hopefully maximise the information accrued, yet avoid the discomfort for patients of undergoing serial biopsies to obtain tumour tissue.

Information from the preclinical models of pancreatic disease developed by Dr Tuveson will soon be integrated into clinical trials. A clinical trial protocol will commence in Cambridge in early 2010 to test novel combinations of gemcitabine and other drugs. Collaboration with Dr Adrian Mander, leader of the MRC Biostatistics Unit Hub in Trials Methodology Research in Cambridge, is providing statistical approaches to maximise the information derived from the trials.

Anticancer cocktails

The unique mirroring arrangement between preclinical models and clinical trials that is being created in Cambridge holds great promise for moving towards individualised therapy for cancer patients. Novel and established drugs can be tested quickly and effectively to work out the appropriate combination that will overcome lack of response to treatment. 'It's now possible to imagine the day,' said Professor Jodrell, 'when each patient is treated with a personalised cocktail of drugs that takes account of the specific attributes of their cancer.'

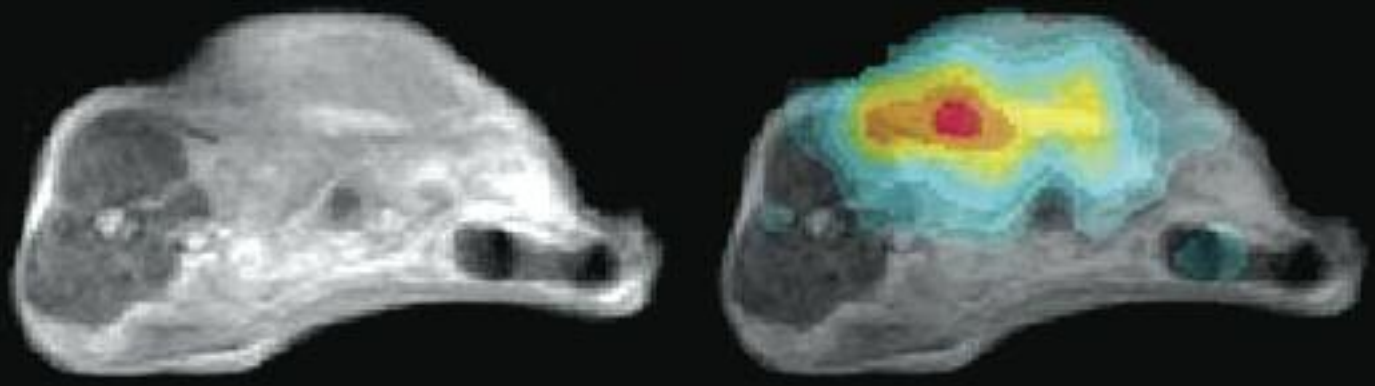


KENNETH P. OLIVE, STEFANIE REICHELT AND MICHAEL JACOBETZ

Recent research shows that the anticancer drug gemcitabine (stained green) is unable to reach pancreatic tumours (stained blue)

Professor Duncan Jodrell (left) and Dr David Tuveson

For more information, please contact Dr David Tuveson (david.tuveson@cancer.org.uk) and Professor Duncan Jodrell (duncan.jodrell@cancer.org.uk) at the Cancer Research UK Cambridge Research Institute/Li Ka Shing Centre (www.cambridgecancer.org.uk/).



PROFESSOR KEVIN BRINDLE

Watching cancer cells eat, breathe and die

Visualising treatment response: lymphoma responding to treatment, imaged using hyperpolarised carbon (red signal indicates greater response)

Cancer cells can now be viewed as never before, thanks to cutting-edge imaging tools being developed in Cambridge.

Increasing the speed and sensitivity of detecting how tumour cells are responding to treatment is something of a Holy Grail in the field of oncology. Treatment response is still largely assessed by looking for a reduction in tumour size using magnetic resonance imaging (MRI) or X-ray computed tomography. But many tumours may take weeks or even months to show evidence of regression and, in some cases, may not regress at all despite a positive response to treatment. How can an earlier indication of response be achieved so that clinicians can select the best treatment for an individual patient?

New techniques are being pioneered in Cambridge to 'see' tumour cells as never before. Research in Professor Kevin Brindle's laboratory is developing a variety of clinically applicable, non-invasive, imaging techniques that measure tumour cells 'eating, breathing and dying'.

Spin doctor

One approach under investigation by the Brindle lab is based on MRI. Although this technique has been around since the 1970s, the new imaging method has a crucial difference – instead of detecting the distribution and properties of water protons in tissue, which conventional MRI does, the new approach detects with much greater sensitivity than ever before the small molecules in tissues that are fundamental to their biochemistry. These are the carbon-based metabolites involved in producing energy and in making the constituents of the cell; a change in how these metabolites are being used can signal that an effective therapy is starting to kill the cells.

The problem with carbon-based molecules is that they are present in tiny amounts compared with the protons in tissue water, making them hard to detect and almost impossible to image at high resolution. To overcome this, the Brindle group has been collaborating with GE Healthcare to develop a technique that increases MRI sensitivity by more than 10,000 times.

To achieve such a dramatic increase in sensitivity, the scientists have turned to nuclear spin hyperpolarisation. Before intravenous injection, a molecule labelled with an MR isotope of carbon is hyperpolarised so that a large proportion of the carbon nuclear spins line up with the magnetic field, as opposed to only a few in a million in a conventional MR experiment. The resulting gain in sensitivity means that the researchers can watch how the hyperpolarised carbon is metabolised by tumours, using this as a read-out for living and dying cells. Data published recently have shown how well this technique works for monitoring treatment response, and the first clinical trials are planned to start in 2010.

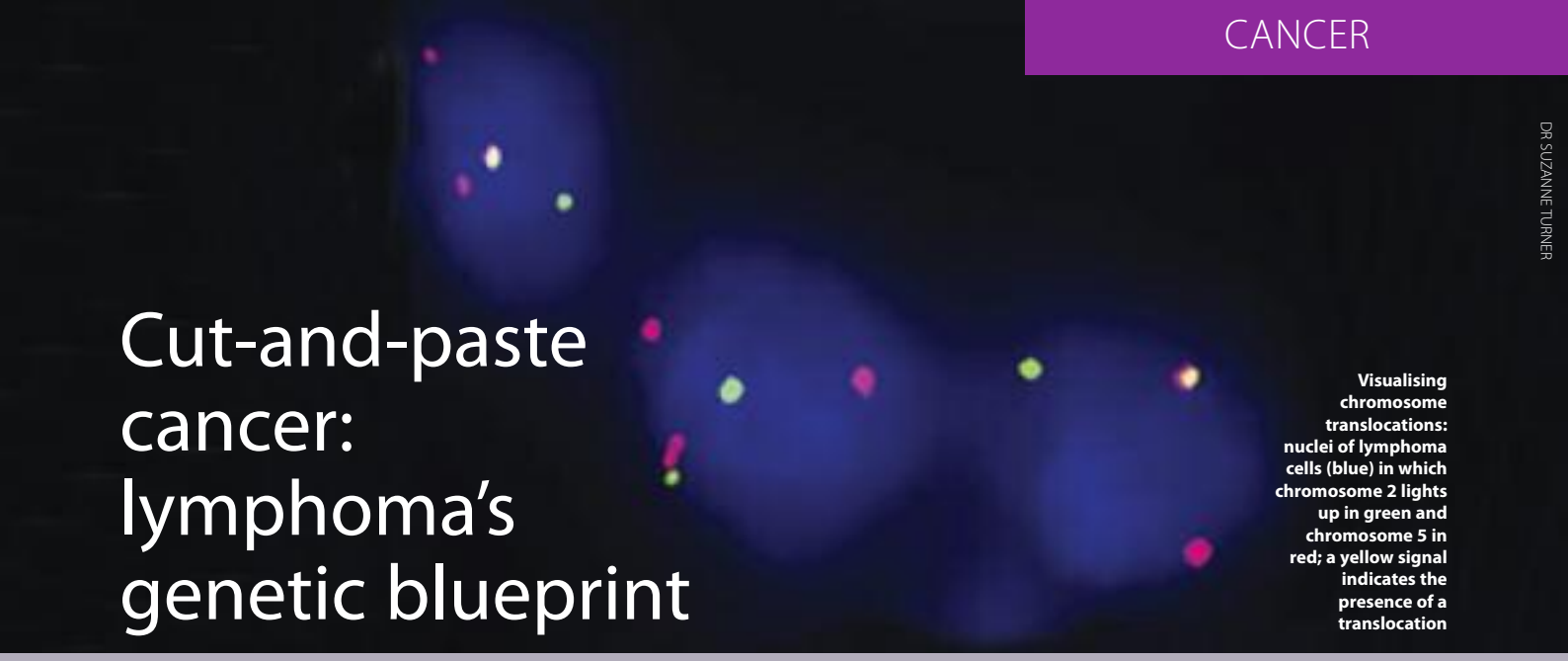
Personalising medicine

Different tumours are likely to require different imaging methods. With recent funding from the Leukaemia and Lymphoma Society, a new study has just begun in which several of the imaging methods under development in the Brindle group are being validated in models of lymphoma (see opposite page), so that the best reagents and protocols can be selected for future clinical trials.

Improved imaging methods are not only useful in the clinic, but will also be invaluable for early stage clinical trials of new drugs, where the need to establish whether new treatments are working is particularly acute. Professor Brindle is working with Professor Duncan Jodrell and Dr David Tuveson at the Cancer Research UK Cambridge Research Institute to develop imaging methods that allow treatment responses in individual patients to be measured immediately (see page 14). Because patients with similar tumour types can show markedly different responses to the same therapy, imaging will be an important component of the armoury of 'personalised medicine', enabling the most effective treatment to be tailored to specific patients.

Professor Kevin Brindle

For more information, please contact Professor Kevin Brindle (kmb1001@cam.ac.uk) at the Department of Biochemistry (www.bioc.cam.ac.uk/) and the Cancer Research UK Cambridge Research Institute/Li Ka Shing Centre (www.cambridgecancer.org.uk/). **This research was published in *Proceedings of the National Academy of Sciences* (2009) 106, 19801–19806 and was funded principally by Cancer Research UK, with material support from GE Healthcare.**



DR SUZANNE TURNER

Cut-and-paste cancer: lymphoma's genetic blueprint

Visualising chromosome translocations: nuclei of lymphoma cells (blue) in which chromosome 2 lights up in green and chromosome 5 in red; a yellow signal indicates the presence of a translocation

Researchers in the Department of Pathology have established precisely how the 'cutting and pasting' of genetic material from one chromosome to another results in cancer.

Lymphoma is an umbrella term that describes cancer of the white blood cells of the lymphatic system, which normally acts to protect the body against infection. In lymphoma, malignant changes in a white blood cell causes it to divide abnormally and out of control; not only are these cells unable to protect the body against infection, and in fact interfere with the growth of healthy cells, but they also build up, often in lymph nodes, as tumours.

Lymphoma accounts for more than 9,000 new cancer cases diagnosed each year in the UK alone and the incidence is rising by about 4% per year. Some of these cases appear to result following viral infections, immunodeficiency or autoimmunity, but for the most part we don't know what causes the genetic alterations underlying the different subtypes of lymphoma, of which over 30 are now known. However, progress is being made in understanding what effect the genetic alteration has on the cell in which it occurs.

Dr Suzanne Turner leads a group in the Department of Pathology who are interested in a subtype of lymphoma that, although rare, has become a paradigm for understanding the growth and development of lymphomas (lymphomagenesis) because of its well-defined genetic alteration.

The many different subtypes of lymphoma have alterations that range from single mutations, through loss and gain in regions of genetic material, to large-scale chromosomal changes. The cancer that interests Dr Turner, anaplastic large cell lymphoma (ALCL), falls into this last category because it results when sections of genetic material from two chromosomes are essentially 'cut and pasted' in the wrong place.

Genesis of a lymphoma

Although relatively rare in adults, ALCL accounts for 1 in 10 cases of all lymphomas in children. The most common type of ALCL is caused by the swapping of genetic material between chromosomes 2 and 5. Rather like the joining together of parts of two different sentences, swapping segments of chromosomes can sometimes result in nonsense. But in some cases, the two parts produce an intelligible outcome, albeit with a different meaning. This is what happens in ALCL: the altered genetic code, which juxtaposes the gene for nucleophosmin (NPM) on chromosome 5 with the gene for anaplastic lymphoma kinase (ALK) on chromosome 2, generates a new gene product (NPM-ALK) at the fusion point between the two chromosomes. Although only portions of the two genes remain, together they create a new protein with altered functions.

Dr Turner's group was one of the first research groups in the world to demonstrate that NPM-ALK can cause cancer. They discovered that the errant protein sets off a cascade of events that confers survival and growth properties on the cells in which it is expressed. The cells proliferate uncontrollably and a lymphoma is born.

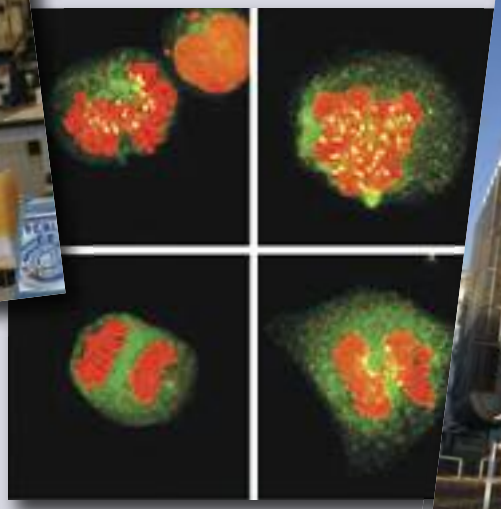
A model system

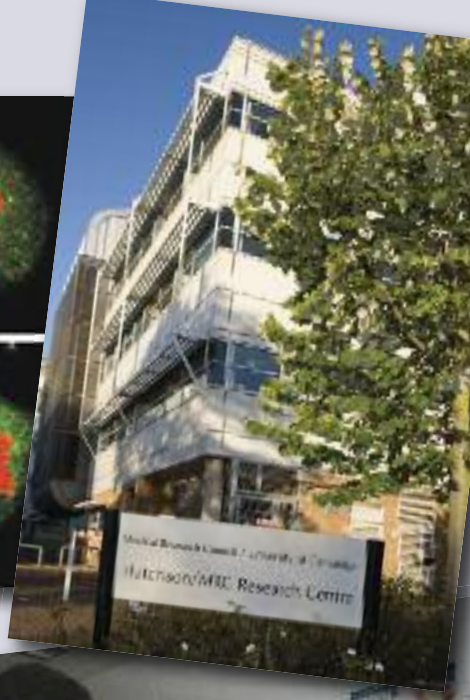
Dr Turner's group has developed model systems to investigate both the specific cell type in which the translocation and disease originate and whether the normal functions of the immune system contribute to the disease process. Potential new drugs and drug combinations, particularly those that inhibit the NPM-ALK protein, are being tested with the long-term aim of taking these into the clinic. A collaboration with Dr Amos Burke, Consultant Oncologist within the Department of Paediatric Haematology and Oncology at Cambridge University Hospitals NHS Foundation Trust, provides an important clinical perspective on the work. And new imaging methods developed by Professor Kevin Brindle in the Cambridge Research Institute (see opposite page) are being used to detect treatment response at an early stage.

For ALCL, the long-term goal is to develop a way of inhibiting NPM-ALK and the catastrophic malignant effects that it initiates within the white blood cell in which it occurs. But these studies will also complete a story – one that explains the way in which lymphoma can be set in motion… and be stopped in its tracks.

Dr Suzanne Turner

For more information, please contact Dr Suzanne Turner (sdt36@cam.ac.uk) at the Division of Molecular Histopathology in the Department of Pathology (www.path.cam.ac.uk/).
Dr Turner is a Leukaemia Research Bennett Fellow and is also funded by the Kay Kendal Leukaemia Fund and Cancer Research UK.





Hutchison/MRC Research Centre

…where fundamental research is pioneering innovative approaches to cancer diagnosis and treatment.

How do different forms of cancer arise? Which individuals are most likely to develop cancer? Why is cancer so difficult to treat? The Hutchison/Medical Research Council (MRC) Research Centre not only addresses these questions through world-class fundamental research, but is also increasingly recognised for translating this information into improved diagnosis.

Integrating science and medicine

The Hutchison/MRC Research Centre was established in 2001 and is jointly directed by Professor Ashok Venkitaraman, Professor Ron Laskey and Professor Sir Bruce Ponder. It occupies a unique niche within the cancer research community in Cambridge because it houses three integrated components that bring together scientists and clinical staff working towards common goals. The MRC Cancer Cell Unit and laboratories of the University's Department of Oncology are carrying out fundamental research on the mechanisms that regulate the division and fate of cancer cells, and are using this information to develop new tools for the early diagnosis of cancers (see opposite). The third component is the Cambridge Molecular Therapeutics Programme, which seeks to create innovative new platforms to make the next generation of cancer drugs (see opposite).

A multidisciplinary approach

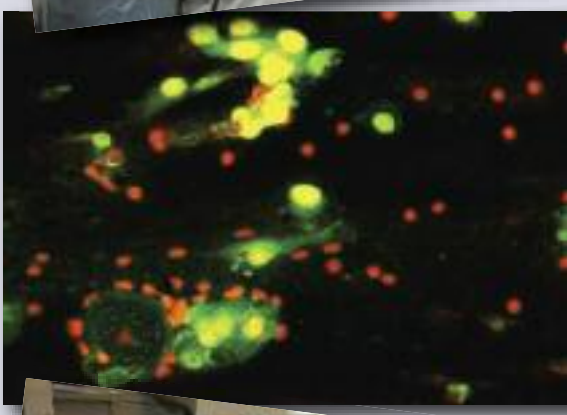
Cancer research today involves a variety of approaches – from chemistry and imaging, to mathematical modelling and cell biology, to clinical investigations and trials. The Hutchison/MRC Research Centre provides an excellent example of the rapid and substantive progress that can be achieved through a multidisciplinary and collaborative approach.

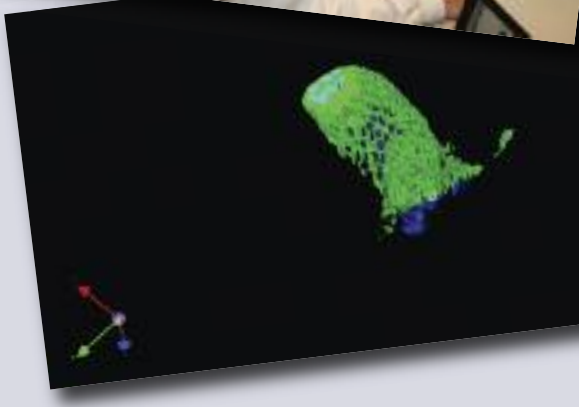
Many groups have strong links to researchers in other University Departments such as Chemistry, Biochemistry, and Applied Mathematics and Theoretical Physics. Bringing these different perspectives to the field of cancer research has had a major impact on our understanding of the disease by contributing new insights into problems as diverse as cell division, protein behaviour and drug discovery.

This integrated, multidisciplinary approach to research also places the Hutchison/MRC Research Centre firmly at the heart of the Cambridge Cancer Centre, whose overall aim is to harness Cambridge's wider strengths in fundamental and applied sciences to improve clinical outcomes for cancer patients. As part of this initiative, the Hutchison/MRC Research Centre will continue to build on its reputation for identifying major clinical problems in the cancer field, addressing these problems using fundamental research, and translating the solutions into diagnostic tools and treatments that improve human health.

Professor Ashok Venkitaraman

For more information, please visit www.hutchison-mrc.cam.ac.uk/





Improving cancer diagnosis

Most common cancers are difficult to treat successfully once the cancer has spread. Scientists at the MRC Cancer Cell Unit in the Hutchison/MRC Research Centre have identified improved methods to detect cancer early.

A major goal in public health is to detect cancer, or pre-cancerous changes, at an early stage using methods that are effective and practical enough to roll out to GP surgeries, medical screening laboratories and developing countries.

'For cancer of the oesophagus,' explained Dr Rebecca Fitzgerald, 'most patients present with symptoms late on, when they are having trouble swallowing. By then, the chance of surviving five years after therapy is only 20%, and yet the first signs of disease in these patients are often visible 10–20 years beforehand.'

'Screening for cervical cancer using the smear test is a prime example of the success of early detection programmes,' added Dr Nick Coleman, 'but cervical changes are subtle and a high degree of training is needed to recognise them. What's needed is an effective way of automating screening.'

Professor Ron Laskey and Dr Coleman have discovered a biomarker that enables screening for differences between normal and diseased cells. Normal cells don't express mini chromosome maintenance (MCM) proteins, whereas cancerous and pre-cancerous cells express them in abundance. Screening for the presence of MCM proteins in cervical smears can substantially improve early diagnosis. The technology has been licensed to Becton, Dickinson and Company, which is running large-scale trials for cervical cancer screening. Meanwhile, the researchers are now investigating the wider application of this tool: in colorectal cancer, in collaboration with Mr Richard Miller, Consultant Colorectal Surgeon in the Department of Surgery, in lung cancer and in anal cancer.

MCM proteins are also being used by Dr Fitzgerald to detect pre-cancerous changes in the oesophagus. Cancer of the oesophagus kills about 7,000 people each year in the UK, and the figure is increasing. Two-thirds of cases develop through a recognisable pre-cancerous stage called Barrett's oesophagus and Dr Fitzgerald has developed a means of detecting this without endoscopy. A sponge on a string is swallowed and is then gently withdrawn up the oesophagus, bringing with it samples of the lining cells to be examined for evidence of biomarkers. Following the success of a pilot study of 500 patients with a history of heartburn (associated with the development of Barrett's oesophagus), a much larger study is being planned to see just how accurate the test is in comparison with endoscopy.

Testing positive to early detection tests will define much smaller groups of individuals who can then be offered specialist investigation and treatment at a very early stage of the disease, when the chances of full recovery are high.

For more information, please contact Dr Rebecca Fitzgerald (rcf29@hutchison-mrc.cam.ac.uk) or Dr Nick Coleman (nc109@hutchison-mrc.cam.ac.uk).

New approaches to cancer drug discovery

The Cambridge Molecular Therapeutics Programme (CMTP) is developing innovative strategies to widen the repertoire of 'druggable' cancer targets and accelerate the clinical development of new medicines.

The discovery and clinical development of new medicines against human diseases such as cancer is long, expensive and inefficient. A major problem is that fewer than 10% of the proteins encoded in the human genome have successfully been 'drugged' using conventional methods, making it difficult to target those linked with cancer. A second is that the failure rate during early clinical development of new anticancer drugs is unacceptably high, largely due to poor understanding of their effects. The CMTP harnesses the strengths of Cambridge academic sciences to address these key challenges, bringing together expertise in chemistry, structural biology, physics and engineering (led by Professors Chris Abell, Tom Blundell and Mike Payne) with the biomedical research in the Hutchison/MRC Research Centre led by Professor Ashok Venkitaraman.

New approaches to widen the repertoire of 'druggable' targets start with the development of novel assay platforms to identify the hard-to-find targets that characterise different forms of cancer. A platform of innovative screening methods is then used to discover chemical 'leads' that can be used against them. These include fragment-based methods, where small fragments (rather than complete drug molecules) are soaked into crystals of the target protein to identify the site and nature of the binding interaction, and this information is used in the design and synthesis of the next generation of inhibitors. Another approach involves novel 'libraries' of drug-like chemicals, which are screened for activity against target proteins by biophysical assays, cell-based assays and *in silico* screens, and elaborated further using structure determination.

The second major strand of work in the CMTP is to accelerate the early clinical development of new anticancer drugs through improved understanding of their effects on normal and cancer cells. Several new approaches are being taken, including the establishment of laboratory models that more accurately predict the effects of drugs on human cancers, and methods to screen for biomarkers that determine which patients are most likely to benefit from the drugs. This work has already led to the design of new types of clinical trials that more effectively match the right drugs to the right cancer patients.

Early success in developing these new approaches has secured over £6 million in funding for the CMTP from sponsors including the MRC and the Wellcome Trust.

For more information about the CMTP, please visit www.cmtp.cam.ac.uk/ or contact Professor Ashok Venkitaraman (arv22@hutchison-mrc.cam.ac.uk), the Ursula Zoellner Professor of Cancer Research.

BioBullets mussel in on water mains

Pipes blocked by an invasion of freshwater mussels pose a severe problem to the water industry. A tiny, fat-coated capsule could provide the answer.

A combination of aquatic ecology and chemical engineering has resulted in a novel means of combating an invasion of zebra mussels into underground water mains. This non-native species originates from central Asia and has become one of the world's most significant environmental pests. In the UK, zebra mussels growing at high density cause problems when they occlude raw water mains that feed water-treatment works, water-cooling systems in power plants and water supplies for drinking.

Dr David Aldridge, from the Department of Zoology, and Dr Geoff Moggridge, from the Department of Chemical Engineering and Biotechnology, have invented an environmentally sound control method called the BioBullet, now being manufactured by their spin-out company BioBullets Ltd.

The fat-coated BioBullet capsule, which is released into the clogged pipe, contains salt-based toxins that are lethal to zebra mussels. The mussels are then flushed out of the water pipe; any BioBullets not taken up by mussels dissolve into harmless components. The technology provides a practical solution that does not affect the treatment process or water quality.

The research has been of great interest to the UK water industry, with four companies funding the research to date. Now, following approval by the Drinking Water Inspectorate, trials have begun with Anglian Water Services Ltd to use the pellets in the UK for potable water systems. A new manufacturing site is under way for BioBullets following an award of £500k by the Technology Strategy Board (TSB), which is being match-funded by Anglian, Thames Water and Tastetech.

Barrie Holden, Water Innovation Manager at Anglian Water, said: 'We are very encouraged that this technology will have a significant impact on the ability of our water treatment works to receive the required volume of raw water by limiting the infestation. The technology potentially provides an economic and environmentally sound solution to a persistent problem.' Dr Aldridge added: 'Working closely with Anglian Water and other water industries is giving us new insight into how best to formulate and deliver the BioBullets solutions.'

DR DAVID ALDRIDGE

Dr David Aldridge and zebra mussels

For more information, please contact Dr David Aldridge (d.aldridge@zoo.cam.ac.uk).

A new model for industrial–academic partnership

PneumaCare, the first company to receive funding from the University of Cambridge Discovery Fund, is a new model for utilising academic expertise.

PneumaCare is solving the problem of how to monitor lung function in babies, children and chronically sick patients using a non-invasive medical device. The idea for the device, which combines innovative image processing with technologies from the gaming and movie industry, has been developed by a consortium of experts that includes Dr Joan Lasenby at the Department of Engineering, Dr Richard Iles at Cambridge University Hospitals NHS Foundation Trust and Dr Colin Smithers of Plextek Ltd.

The company represents a new and interesting departure from the usual spin-out model, as Dr Gareth Roberts, PneumaCare Chief Executive, explained: 'Recognising an unmet medical need, the company consulted and utilised University expertise to create an innovative product. We have developed a close working relationship with the academics involved and, to cement this relationship, the academic partners have become equity holders. The success of this model ensures that the University shares in the company's success.'

PneumaCare will present data from its first product, PneumaScan™, over the next few months. 'We believe that the PneumaScan will make monitoring feasible, effective and simpler, leading to better patient recovery,' said Dr Roberts. 'We have generated considerable interest in the investment community and are poised to go into full clinical development and medical trials.'

Part of this investment has come from the newly created University of Cambridge Discovery Fund, which is managed by Cambridge Enterprise Ltd. The fund was created to smooth the path of transferring University-related technologies for the benefit of society by providing proof of concept, pre-licence, pre-seed and seed investments, and is capitalised from donations through the University of Cambridge 800th Anniversary campaign.

For more information about PneumaCare, please visit www.pneumacare.com/
For more information about the University of Cambridge Discovery Fund, please contact Cambridge Enterprise Ltd (Tel: +44 (0)1223 760339; email: enquires@enterprise.cam.ac.uk) or visit www.enterprise.cam.ac.uk/

A measure of prison performance

Pioneering research by Cambridge criminologists is helping prison managers to understand what makes a good prison.

The Prisons Research Centre in Cambridge's Institute of Criminology has been working in and with prisons for the past decade, carrying out a programme of empirical research that is helping to inform policy and operational decision making in prisons.

'All prisons have strengths and weaknesses,' explained Centre Director Professor Alison Liebling, 'but how prison authorities go about objectively evaluating the quality of prisons has suffered from a lack of systematic research on what matters most, and has failed to link differences in prison organisation and culture to outcomes such as suicide and reconviction.'

Aiming to fill this gap, Professor Liebling and colleague Dr Ben Crewe have spent almost three years interviewing senior managers, staff and prisoners at public and private prisons across the UK. The study, funded by the Economic and Social Research Council (ESRC), draws on the trust and credibility they have developed over many years through engagement with practitioners and prisoners.

In piecing together the complex interplay of values, practices and outcomes that define the relative success and failure of prisons, the net result of this study, building on several others, has been the development of a survey-based management tool with which prisons can now measure their own performance. 'Using the tool, we've found some really clear patterns that show what makes an establishment work well and where there is cause for concern,' explained Professor Liebling. 'The prison managers we've worked with have been extremely receptive and are using the data as a basis for strategic planning.'

Phil Wheatley, Director General of the National Offender Management Service, which is responsible for delivering prison and probation services on behalf of the Ministry of Justice, added: 'This research has enabled the Prison Service to better understand how prison management can be more effective and to better understand the complexity of the prison officer role. Specific deliverables include a new anti-suicide policy, which has substantially reduced suicide, and a survey for measuring prisoner perceptions, which has been used to judge the success of our prisons.'

For more information, please contact Professor Alison Liebling (al115@cam.ac.uk).

Innovative tool reveals the paintings hidden within

The development of optics that 'fly' over paintings could revolutionise art conservation.

CHRIS TITMUS

SatScan in operation

An innovative tool to image artwork has resulted from a partnership between art conservators at the Hamilton Kerr Institute (HKI), a research department of The Fitzwilliam Museum, and SmartDrive Ltd, a Cambridge-based company that specialises in precise motor control systems.

SmartDrive usually work with electromechanical companies needing precise motion control for robotic assembly lines and scientific instrumentation. But for this venture, they turned to the HKI, a centre of excellence for conservation services and world renowned for its research on oil and tempera easel paintings.

The aim of the joint venture was to use tools that SmartDrive had developed for science and technology applications to create a scanning system to guide art conservation. The result, SatScan, is capable of revealing hidden layers of paint, as Chris Titmus, imaging consultant at the HKI, explained: 'The information that SatScan provides guides the restoration process and enriches the history of the work. It can also help with authentication by revealing details that may show consistency with a certain artist.'

Detailed topographical surface data from the artwork are captured using a moving camera that, under computer control, 'flies' in front of the painting. High-resolution digital images in visible light, infrared and ultraviolet parts of the spectrum are used to visualise under-drawings or to examine previous re-touching. The system speeds up a previously manual, cumbersome process and extends the size and range of work that can now be scanned.

Dennis Murphy, Managing Director of SmartDrive, said: 'Without HKI's expert knowledge of the area, and capacity to put SatScan through its paces in a working environment, we could never have developed a tool that we feel is a significant breakthrough for art restoration.'

For more information, please contact Chris Titmus (cjt50@cam.ac.uk) or visit www-hki.fitzmuseum.cam.ac.uk/ or www.smartdrive.co.uk/

The book publishing industry has gone through more change during the past few decades than in any comparable period in its 500-year history. Professor John Thompson examines this change and asks what impact it will have on the future of books.

The future of books

For centuries, books have played a central role in education, the spread of knowledge and the cultivation of literary and scholarly debate. With its origins dating back to the 15th century, the publishing of books is the oldest of the media industries and one which has continued to flourish despite the profusion of other media forms. However, over the last 30–40 years, the industry has gone through a process of turbulent change stemming from forces that are partly commercial, partly technological. Thanks to these developments, it bears little resemblance today to the industry that existed in the 1960s and before.

Despite these changes and despite the continuing importance of books in contemporary culture, there has been very little systematic research on the modern book publishing industry. Historians have studied the book trade and the impact of books in earlier centuries, but the modern publishing business has been largely neglected by researchers.

It was partly to fill this gap in our knowledge that I began in 1999 to study the changing structure of the industry in Britain and the United States. The research, spanning a decade, was funded by two grants from the Economic and Social Research Council (ESRC). While the first phase of the research focused on academic publishing, the second phase, begun in 2005, was concerned with mainstream trade publishing – the world of general interest books, aimed at the wider public and sold through high-street bookstores, supermarkets and the internet. This is the sector of publishing that produces bestsellers like Dan Brown's *The Da Vinci Code* – books that are widely reviewed in the press, prominently displayed in bookstores and, in some cases, turned into films.

What makes a bestseller? Why do some books take off and become runaway successes while thousands of others vanish without a trace? What are the changes that have swept through the industry and how have they affected the nature of what gets published and what succeeds? What impact have these changes had on the character of our literary culture, and what impact are they likely to have in the years to come?

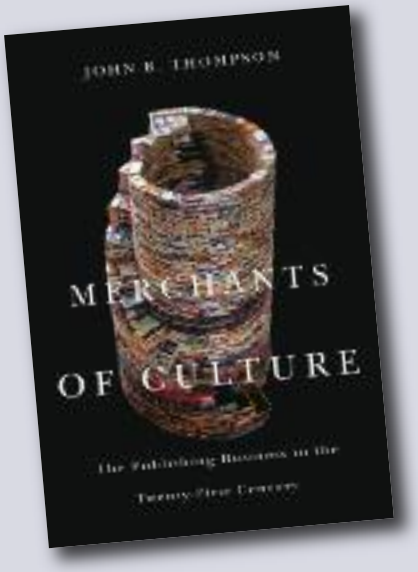
Three key developments

To address these and other questions I immersed myself in the world of trade publishing in Britain and the USA. I interviewed senior managers, editors and other staff at all of the large trade publishing groups in London and New York, as well as many staff working in small and medium-sized publishing houses; I also interviewed agents, authors, scouts and booksellers – altogether, I did more than 250 interviews with key players in the industry. This enabled me to build up a detailed picture of how the industry works, how it has changed over the past few decades and how it is changing today.

I was able to show that three key developments have shaped the evolution of trade publishing in the English-speaking world since the 1960s. The first was the growth of the retail chains, like Waterstones in the UK and Barnes & Noble in the USA. These nationwide chains of book superstores transformed the landscape of bookselling in the 1980s and 1990s; they made books much more widely available, but at the same time they drove many smaller independent booksellers out of business.

The second development was the rise of the literary agent. Although not new – the first agents appeared in London at the end of the 19th century – literary agents have, since the 1970s, become much more powerful brokers in the field of trade publishing. They control access to new content and, through auctions, are able to raise the stakes for books that are perceived to have high sales potential.

The final development was the consolidation of publishing houses under the umbrella of large multimedia corporations. Many of the great



Merchants of Culture: the Publishing Business in the 21st Century **by Professor John B. Thompson will be published in 2010 by Polity**

publishing houses whose names are well known to us all – Penguin, Jonathan Cape, Macmillan, Knopf – are today owned by large corporations and survive as imprints rather than as independent publishing houses.

Making bestsellers

Together, these developments have created a field of cultural activity that has a distinctive structure and dynamic – a 'logic of the field'. They have led, for instance, to the polarisation of the industry, with four or five large corporate groups dominating the field and a plurality of small independent publishers on the margins. Very few medium-sized independent publishers remain active: in this new world of trade publishing, it is very difficult to be medium-sized.

These developments have also led to a preoccupation with what in the industry are commonly known as 'big books'. These are not yet bestsellers but rather 'hoped-for bestsellers'. Given the unavoidable role played by serendipity in trade publishing, it is simply unclear how well many new books will do in the marketplace – no-one really knows.

So how do publishers decide how much they're willing to pay for them? Various factors come into play here, but a crucial role is played by 'the web of collective belief' which is built up through the numerous conversations that take place between agents, editors and other players in the field. In the absence of anything solid, the expressed enthusiasm (or lack of it) of trusted others is decisive.

The focus on big books is exacerbated by the financial pressures on the publishing houses owned by large corporations and by the practices of the retail chains, which order large quantities of some new books, charge publishers a premium for front-of-store displays and expect them to turn over quickly. Many new books fail to take off and are sent back to publishers in large numbers, resulting in historically high levels of returns. But in those cases where they do take off, publishers and booksellers mobilise quickly behind them, with additional resources and promotion, pouring more fuel on the flames – this in part is how bestsellers are made.

The end of the book?

Today trade publishers are faced with unprecedented challenges. The economic climate is tough, overall sales (especially in North America) are down and the arrival of a new generation of ebook readers has raised fresh questions about the future of printed books. Do these developments mean that the world of the book as we've known it is about to undergo a further transformation, even more radical than that which has characterised the industry in recent decades, perhaps even leading to the eclipse of the printed book as such?

Despite widespread speculation about the 'end of the book', we are still a long way from a world in which trade books are routinely read on screens rather than on the printed page. Although ebook sales have increased significantly in recent years, especially in the USA, they still account for only around 1% of the revenues of trade publishers – a tiny fraction. This is bound to increase as reading devices become more widely available but no-one knows exactly how significant it will eventually become.

Whatever happens, it seems likely that books will continue to play an important role in our cultural and public life for the foreseeable future. Books have been, and remain for many, a privileged form of communication, one in which the genius of the written word can be inscribed in an object that is at once a medium of expression, a means of communication and a form of art. For the telling of extended stories or the sustained interrogation of our ways of thinking and acting, the book has proven to be a most satisfying and resilient cultural form, and it is not likely to disappear soon. But how books will be produced and delivered, and where they will fit in the new symbolic and information environments that are emerging today, are questions to which there are, at present, no clear answers.

Professor John Thompson

For more information, please contact the author Professor John Thompson (jbt1000@cam.ac.uk) at the Department of Sociology (www.sociology.cam.ac.uk/).

Britain's island heritage: reconstructing half a million years of history

The latest instalment of a 20-year study to understand how Britain became an island completes a tale of megafloods and super-rivers.

Deep below the Bay of Biscay, where the English Channel meets the Atlantic Ocean, layers of sediment hold precious information about how Britain came to be separated from mainland Europe. Until recently, the clues had remained hidden, off limits owing to the impracticalities and cost of obtaining long-piston core samples and high-resolution acoustic data in this area. However, thanks to an Anglo-French collaboration between Professor Phil Gibbard, who leads the Quaternary Palaeoenvironments Group in the Department of Geography, and PhD student Sam Toucanne and his colleagues from the University of Bordeaux, the seabed has now yielded its secrets. In doing so, it provides the final instalment in a story that has been unfolding for two decades, since Professor Gibbard first began his detailed palaeogeographic and paleoenvironmental reconstructions of the southern North Sea.

When Britain actually was in Europe

But the story really starts 500,000 years ago, five ice ages before present times, when Britain was connected to Europe through a land mass that stretched from The Netherlands to the Dover Strait. Between Britain and France was a wide shallow area into which southerly rivers like the Somme and the Seine drained, while the Thames and the Rhine drained northwards into the North Sea.

Indications as to what happened to the landmass over the ensuing half a million years have been found in sedimentary investigations of the geological history of the southern North Sea region and neighbouring areas by Professor Gibbard. These provided a read-out of past environments, including climatic changes, and of how and where the rivers flowed during the past. Together with bathymetric maps (sonar readings of the floor of the English Channel, showing the topography of deep valleys running the length of the waterway), it has been possible to build up a detailed picture of the conditions of the region: where rivers drained, glaciers formed and landmasses changed.

Most recently, the scientists have been able to build up a continuous record of the Earth's climate variability for the past 1,200,000 years, showing a correspondence between temperature changes caused by the waxing and waning of the glaciers and the peaks and lows in sedimentary deposits. The data show that three of the five ice ages – 450,000 years, 160,000 years and 30,000 years ago – seem to have had the most dramatic impacts on the sedimentary deposits. Could one or more of these ice ages have precipitated the events that resulted in Britain becoming separated from Europe?

The Dover Strait was formed in the last half a million years when a massive lake, dammed to the north by the European ice sheet, burst through into the English Channel

Megafloods and super-rivers

The first breakthrough came when Professor Gibbard's investigations of the southern North Sea region and review of the drainage systems led him to suggest the existence some 450,000 years ago of a massive lake. The meeting of a glacier flowing down across Britain from the north and a glacier advancing from Denmark strongly modified the flow directions of central European rivers, effectively blocking their flow into the Atlantic Ocean. The result was the build-up of a large, freshwater, glacial lake, about the size of East Anglia, just north of what is now the Dover Strait. The lake was dammed by an ice sheet, landmass and, crucially, the upfolded spit of land that linked Britain and France at the Dover Strait.

The first morphological evidence came to light in 2007 from bathymetric maps of the English Channel. Dr Sanjeev Gupta at Imperial College London observed that the existence of long grooves of erosion and deep valleys running longitudinally along the bedrock floor fitted with an extraordinary conclusion. It seems that the freshwater lake filled until, like an overflowing bath, it breached the Dover Strait. A catastrophic discharge of water surged at least once and probably twice down the basin between Britain and France, overwhelming the rivers and streams below it, and spreading out across the basin as a megaflood. This massive southwards discharge of meltwaters merged with the river-water from the Seine, Somme and others, to form the 'Fleuve Manche' (Channel River) palaeoriver, one of the largest river systems on the European continent.

Further ice ages followed. Each time, as the glaciers receded, sea levels rose and the Channel would continue to be carved out; as glaciers returned, sea levels dropped and the landmass would once more connect Britain to the Continent. A second megaflood seems to have happened 160,000 years ago, only this time the gap at the Dover Strait was enlarged enough that it would never reform: Britain was now an island.

A full reconstruction

The recently published Anglo-French study has provided the final piece of the puzzle by looking, for the first time, at what flowed out of the Channel into the Bay of Biscay during these crucial periods of Quaternary history. Corroborating the story that had emerged from the upstream sedimentary analyses and the bathymetric data, this new research demonstrates peaks and troughs in the character and volume of the sedimentary material relating to the interglacial and glacial periods. Significantly, at the times identified for the megaflood, the scientists found that the volume and character of the sedimentary material vastly increased, consistent with massive surges in ice-rafted debris and sediment having swept down the Fleuve Manche super-river and out into the Bay of Biscay. With this new research, there is now a complete record that reconstructs these dramatic and far-reaching events that were to give Britain its island status.

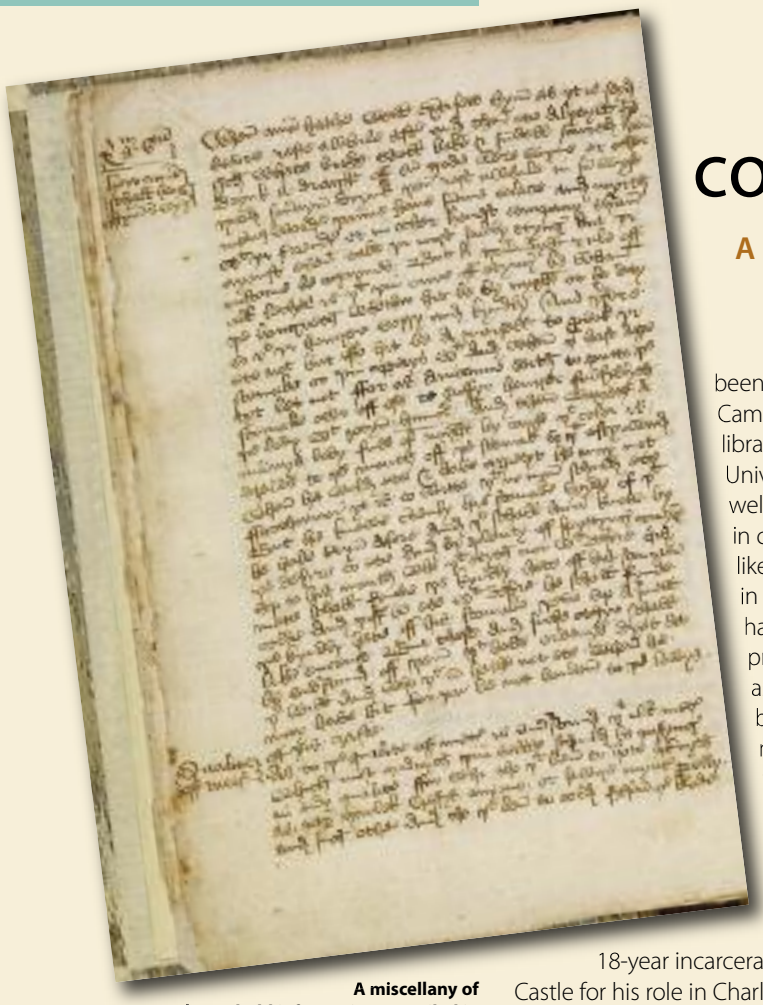
Like any other large-scale geographical upheaval, the implications of the megaflood are profound. The large volume of freshwater released into the Atlantic would have caused changes in ocean circulation, with knock-on effects on the climate in an area stretching from the Bay of Biscay to North Africa. Flora and fauna (including early humans) would also have been affected: during interglacial periods such as the one we are currently experiencing, the high sea level would cut Britain off from mainland Europe, forming a barrier to the migration of humans, animals and plants alike. But in glacial periods, the water level would fall and, although there would never again be a continuous landmass linking Britain with Europe, the Channel River would provide a major migration routeway. In fact it was probably possible to wade across from France to Britain as few as 9,000 years ago, and this may yet be possible tens of thousands of years from now, when we enter the next ice age.

Professor Phil Gibbard

For more information, please contact Professor Phil Gibbard (plg1@cam.ac.uk) at the Quaternary Palaeoenvironments Group (www.qpg.geog.cam.ac.uk/) in the Department of Geography. This research was published in *Quaternary Science Reviews* (2009) 28, 1238–1256 and *Nature* (2007) 448, 259–260.

A scriptorium of commonplace books

A digital archive of 500-year-old 'filofaxes' offers extraordinary insight into early thought and writing practices.



A miscellany of household information compiled in the 15th century; MS Ll.1.18.9v

'Scriptorium' is the culmination of a three-year project in the Faculty of English to digitise and preserve a type of manuscript book well known in 15th- to 18th-century Europe: the commonplace book or manuscript miscellany. And at the heart of the project, which was funded by the Arts and Humanities Research Council (AHRC), lies an innovative tool that will help you to read them.

A literary phenomenon

Commonplace books were the personal organisers of their day. Learned men (and, more rarely, women) would compile books containing recipes, accounts, sonnets, quotes, prayers, songs, legal treatises and medical instructions. Sometimes passed from one owner to another and continued over decades, if not centuries, commonplace books would be filled with snippets of contemporary information and culture. The keeping of such books was regular practice in the period, enabling their owners to record and remember what they had read, been told or overheard. Each is a unique collection of knowledge: an intellectual scrapbook, the filofax of its time.

A total of 20 commonplace books and miscellanies forms the backbone of the Scriptorium project. These books have been sourced from Cambridge college libraries and the University Library, as well as from archives in country houses like Holkham Hall in Norfolk. Some have a known provenance, such as a 17th-century book of estate management written by William Heveningham, part of which was written during his 18-year incarceration in Windsor Castle for his role in Charles I's execution. The Glastonbury miscellany (c. 1450), a 114-page collection of literary texts in Latin and English, started life as a Glastonbury monk's accounts book and, after successive interventions by five more scribes, was still being added to a century later.

Daleks aid digitisation

Over the course of three years, the project team, led by Drs Richard Beadle, Raphael Lyne, Andrew Zurcher and Colin Burrow, adapted and developed painstaking techniques to minimise the risk of damage to texts during photography. 'Daleks', made from an aluminium bolt and two sewing needles, provided one means of safely applying adjustable levels of pressure on manuscript leaves, to lay them flat for photography. Project researchers, including Drs Christopher Burlinson, Angus Vine and Sebastiaan Verweij, also pioneered new descriptive methods and representational strategies for publishing rare manuscript materials online, including full and searchable analyses of each manuscript, and transcriptions of key selections.

Working in collaboration with the Centre for Applied Research in Educational Technologies (CARET), and IT developer Mariko Brittain, the team also developed an expansible, automated manuscript image database that will continue to function and grow beyond the life of the funded project. And with conservation in mind, high-resolution manuscript images have been securely dark-archived in DSpace@Cambridge, Cambridge University Library's digital repository.

Help with handwriting

The art of deciphering old handwriting, known as palaeography, is a difficult decoding process that can be complicated by factors such as the scribe's style, evolving letter-forms and unusual punctuation. Help in cracking this code is now available from the Scriptorium project's fully interactive online English Handwriting course. The course makes full use of the wide range of hands, styles and idiosyncratic habits represented by the Scriptorium project manuscripts, which were chosen with an eye to their palaeographical range and complexity.

This and other resources within the Scriptorium project are dovetailing with teaching and research in the Faculty of English, opening up the literature, history, theology and philosophy of earlier periods to a new generation of students and scholars in Cambridge and across the world.

Dr Raphael Lyne, Dr Richard Beadle and Dr Andrew Zurcher (left to right)

For more information, please contact Dr Richard Beadle (rb243@cam.ac.uk), Dr Raphael Lyne (rtrl100@cam.ac.uk) and Dr Andrew Zurcher (aez20@hermes.cam.ac.uk) at the Faculty of English or visit Scriptorium (http://scriptorium.english.cam.ac.uk/).

Le bon usage: using French correctly

The purity and linguistic correctness of the French language has been closely guarded by the French for centuries. Professor Wendy Ayres-Bennett is exploring the reasons behind this national preoccupation.

In these globalised times, when international communication has taken some endangered languages to the point of extinction, it is fascinating to consider how one nation has resisted the encroachment of other languages in the interests of keeping its language pure.

The French have long been keen advocates of linguistic correctness or 'good usage'. Indeed, it is often said that France provides the most extreme example of a prescriptive, interventionist and purist attitude to use of language. Even today, ministerial commissions recommend acceptable terminology for fields as diverse as IT and nuclear energy, and the Académie française (the French language academy) advises on proper usage of French vocabulary and spelling, as it has done since the 17th century.

In a major research project funded by the Arts and Humanities Research Council (AHRC), Professor Wendy Ayres-Bennett is directing a collaborative project researching the origins of this concern for linguistic correctness and the broader symbolic values associated with it.

Remarks and observations

The French preoccupation with language purity is reflected in the founding of the Académie française in 1635 and, perhaps above all, in the publication of a particular type of metalinguistic work. In 1647, Academy member Claude Favre de Vaugelas published his *Remarques sur la langue française*, a collection of short, randomly ordered remarks and observations intended to resolve points of doubtful usage and provide clear guidance on the good use of French.

Vaugelas's book quickly became a bestseller and was highly influential. We know, for instance, that in 1660 the great playwright Pierre Corneille reworked the language of his plays to take account of Vaugelas's judgements and that Jean Racine, author of some of France's finest tragedies, is said to have taken a copy of the work with him to the south of France so as not to become 'contaminated' by regional speech.

To understand the appeal and influence of such works in their day and beyond is to examine the social and cultural history of France. In a period of great social mobility, when nobility could be purchased by the newly rich, the volumes acted as a kind of linguistic courtesy book. Someone arriving new to the King's court would need to know not only how to dress and eat properly, but perhaps above all how to speak correctly, so as not to offend polite society.

A rich resource

Many volumes of remarks and observations have been published by various authors down the centuries. All are typically intended not for foreigners but for competent native speakers who wish to perfect their usage of French.

These volumes provide the focus of the research project, which brings together scholars from North America, France and other parts of Europe to address key questions about the genre and to create a corpus of the principal texts, to be published online and as critical editions. This valuable research tool will provide those working on contemporary French with a historical perspective to their research: many of the most troublesome rules of French grammar used today, including past participle agreement, date from these early remarks on the French language. Moreover, one of the most fascinating aspects of the research is that the volumes of remarks provide unique data on how people actually wrote and spoke in the period.

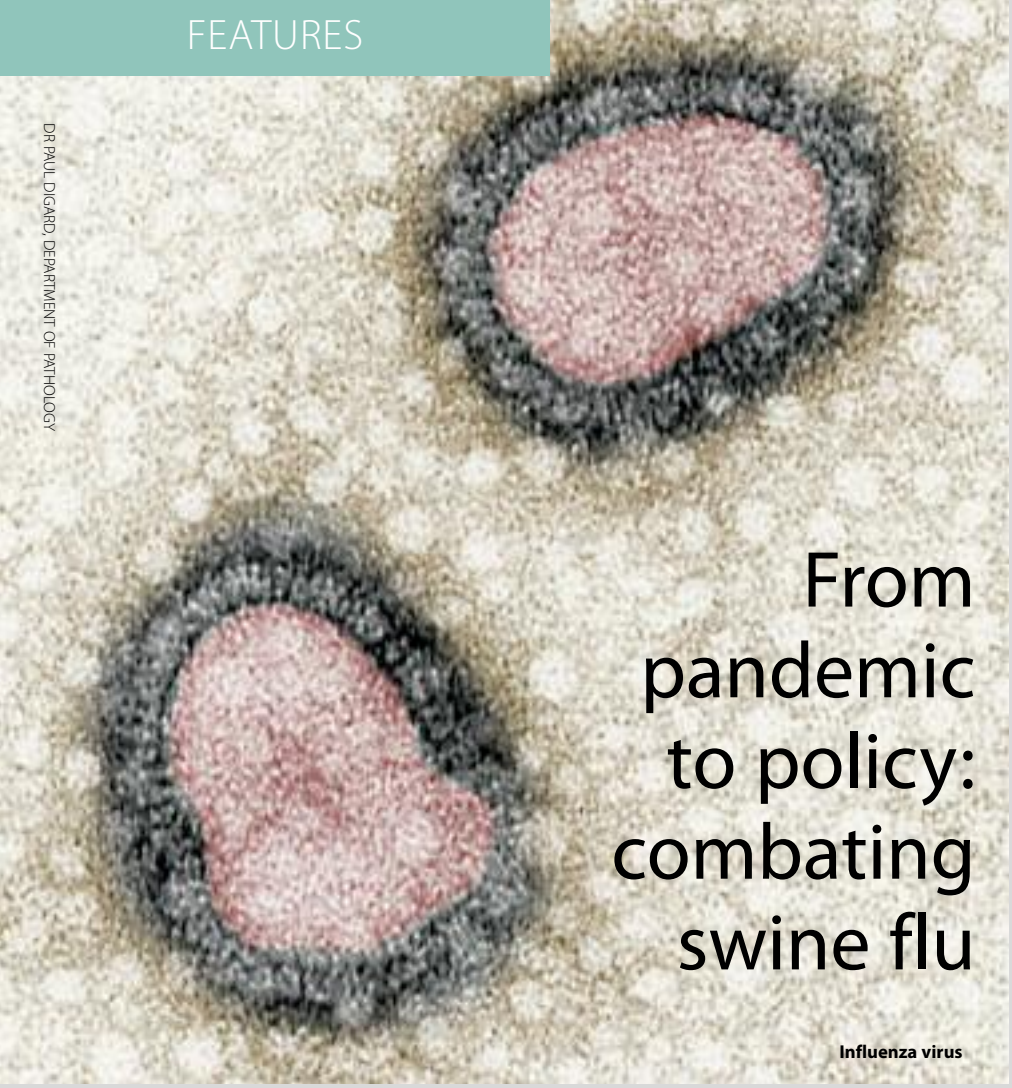
PROFESSOR WENDY AYRES-BENNETT

Frontispiece of Vaugelas's *Remarques sur la langue française* (1647)

The writers of remarks continually strived to define what is French and to exclude the unwanted 'other', whether this is regional, low-register or foreign usage. Notions of language, nation and identity are thus closely intertwined. In short, to research the history of standardisation and linguistic correctness in France involves consideration of what it is to be French.

Professor Wendy Ayres-Bennett

For more information, please contact the author Professor Wendy Ayres-Bennett (wmb1001@cam.ac.uk) at the Department of Linguistics (www.mml.cam.ac.uk/ling/).



DR PAUL DIGARD, DEPARTMENT OF PATHOLOGY

From pandemic to policy: combating swine flu

Influenza virus

'This is amongst the fastest I have ever seen the UK science community react to an emerging disease threat. Turning around a funding initiative in a matter of months while ensuring we are supporting the best science has been a huge achievement by the scientific community and the funders.'

Professor Douglas Kell, BBSRC Chief Executive, commenting on four new collaborative projects being funded across the UK, one of which is being led by Cambridge.

Pandemic H1N1 virus infection – or 'swine flu' – has spread globally following its emergence in Mexico in March 2009. Millions of people have been infected and, as of December 2009, over 9,500 deaths have been reported to the World Health Organization (WHO).

Governments and individuals are understandably concerned: this is the first human influenza pandemic in more than 40 years. Although a 'bird flu' pandemic has been feared since 1997, no more than a few hundred people died of avian H5N1 influenza, despite being spread by migratory birds and the international poultry trade. Putting this in context, hundreds of thousands of people globally continue to die from seasonal influenza each year.

Not only do severe pandemics have far-reaching repercussions for human health, the health sector and the economy, but influenza outbreaks in farmed animals also have a profound impact on the consumer market and loss of business. New research on the origins, spread and prevention of swine flu is urgently needed to inform government policy on how future pandemics like the one we are currently experiencing can be detected, controlled and ultimately prevented.

A coordinated research response

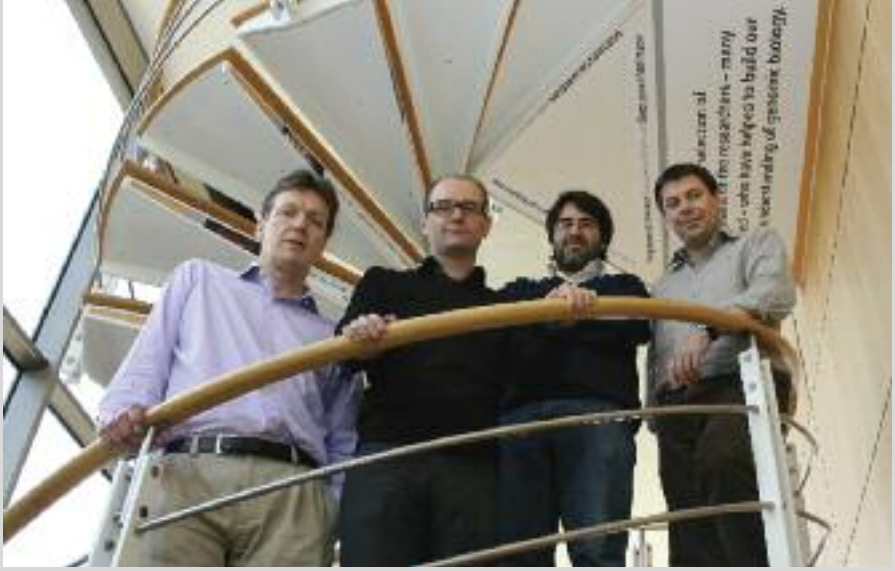
In what has been described as among the fastest reactions of the UK science and funding community to an emerging disease threat, leading UK research funders announced in November 2009 funding of £7.5 million aimed at understanding the development and spread of pandemic influenza. This coordinated response from the research community was catalysed by the Medical Research Council (MRC), Wellcome Trust, Biotechnology and Biological Sciences Research Council (BBSRC), Department of Health and Department for Environment, Food and Rural Affairs (Defra). The result has been the funding of four major collaborative projects (see panel).

In Cambridge, Professor James Wood at the Department of Veterinary Medicine leads a study to monitor the spread and evolution of influenza in infected UK pig herds and farm workers, bringing together a multidisciplinary team of 18 researchers from Cambridge, Oxford, Edinburgh and London. A sister project led by Professor Ian Brown at the Veterinary Laboratories Agency (VLA), Weybridge, focuses on the transmission, infection dynamics and immunopathology of H1N1 in pigs compared with human infection. Together, the two projects form the Combating Swine Influenza (COSI) Initiative.

Viral 'mixing vessels'

The new research builds on a programme of study carried out by the Cambridge Infectious Diseases Consortium (CIDC), which has been investigating infectious animal viruses that pose a major disease threat to both animal and human populations. The CIDC is led by Professor Wood in the Department of Veterinary Medicine and operates in close collaboration with the Animal Health Trust (AHT) in Newmarket.

A large part of research within the CIDC focuses on swine H1N1 and equine H3N8 viruses. Swine flu is common in pigs in Europe and circulates through farms on at least an annual basis. Equine influenza virus also circulates endemically in the UK, predominantly affecting younger horses. Working closely with the international and national reference laboratories for swine and equine influenza – the VLA and the AHT, respectively – and collaborating with the Wellcome Trust Sanger Institute, researchers at the CIDC are aiming to examine genetic variation within endemic viruses.



Scientists from the Department of Veterinary Medicine and the Wellcome Trust Sanger Institute will be working together to understand swine flu; left to right: Professor James Wood, Dr Greg Baillie (Sanger), Dr Pablo Murcia, Dr Paul Kellam (Sanger)

This latest strain of swine flu, for instance, is known to have arisen from the combination of two swine influenza viruses, one originating in the USA and the other in Europe. It seems that progenitor viruses were circulating undetected, probably in pigs, for around nine years before the jump to humans took place. Pigs are especially likely to be a 'mixing vessel' for viruses because they are more susceptible to a range of influenza viruses than most other animals.

By examining genetic variation within endemic swine and equine viruses, the scientists hope to understand how virus variants, which usually arise at a low frequency, end up being spread between animals and populations. Using epidemiological and experimental data, they are constructing mathematical models of virus infections, examining questions relating to the control of infection within the host animal, the spread and control of viruses through populations and how the gradual evolution of the influenza virus reaches a threshold before large-scale outbreaks or epidemics are likely to be observed.

The COSI Initiative

The newly funded research initiative is intended to develop a vital new understanding of how the pandemic H1N1 virus behaves in pig populations and how interaction with farm workers may help it to evolve and spread. With this information, it should be possible to move a step closer to developing strategies to slow or prevent the spread of the virus in both pig herds and the human population.

The collaboration led by Professor Wood aims to define the consequences of what would happen if the pandemic H1N1 virus spreads from humans to pigs, as has happened in countries as diverse as Argentina, USA, Canada, Northern Ireland and Australia, probably following the infection of pig farmers who have then transmitted the virus to pigs. In Britain, many pigs are farmed in large populations and, if these farms were to become infected with the pandemic flu virus, then large amounts of virus would be produced with unpredictable consequences.

Detailed genetic studies of archived samples from previous swine influenza outbreaks will be carried out, as well as an investigation of the health of pig farmers and vets who are exposed through their occupation to these outbreaks. This will provide a better explanation of how the pandemic virus arose and spread, including where the initial virus combination took place. With this information, the likelihood of similar events reoccurring can be predicted and recommendations for minimising the ongoing risk can be made.

Another important area will be to predict the immediate threat if the pandemic virus mutates to become a more virulent form, particularly if pandemic H1N1 becomes endemic in the pig population. The rates of viral mutation will be studied and any specific virus mutations associated with the spread between pigs and people working with pigs will be identified. Data from affected farms will be used to make accurate models of transmission and dynamics to help inform intervention strategies.

Informing policy

Together, the four newly funded collaborative projects aim to understand how the virus mutates and jumps the species barrier and how it spreads through communities; how the virus causes disease in both pigs and humans and why it affects some individuals more than others; and which interventions are most effective at preventing infection or treating the disease. The intention is for the results to feed directly into wider policy analysis on dealing with pandemics, for the long-term benefit of human and animal health.

Professor James Wood

For more information, please contact Professor James Wood (jlnw2@cam.ac.uk), the Alborada Professor of Equine and Farm Animal Science, at the Department of Veterinary Medicine, or visit the CIDC website (www.vet.cam.ac.uk/cidc/).
The COSI Initiative is funded by the BBSRC, Defra, MRC and Wellcome Trust.

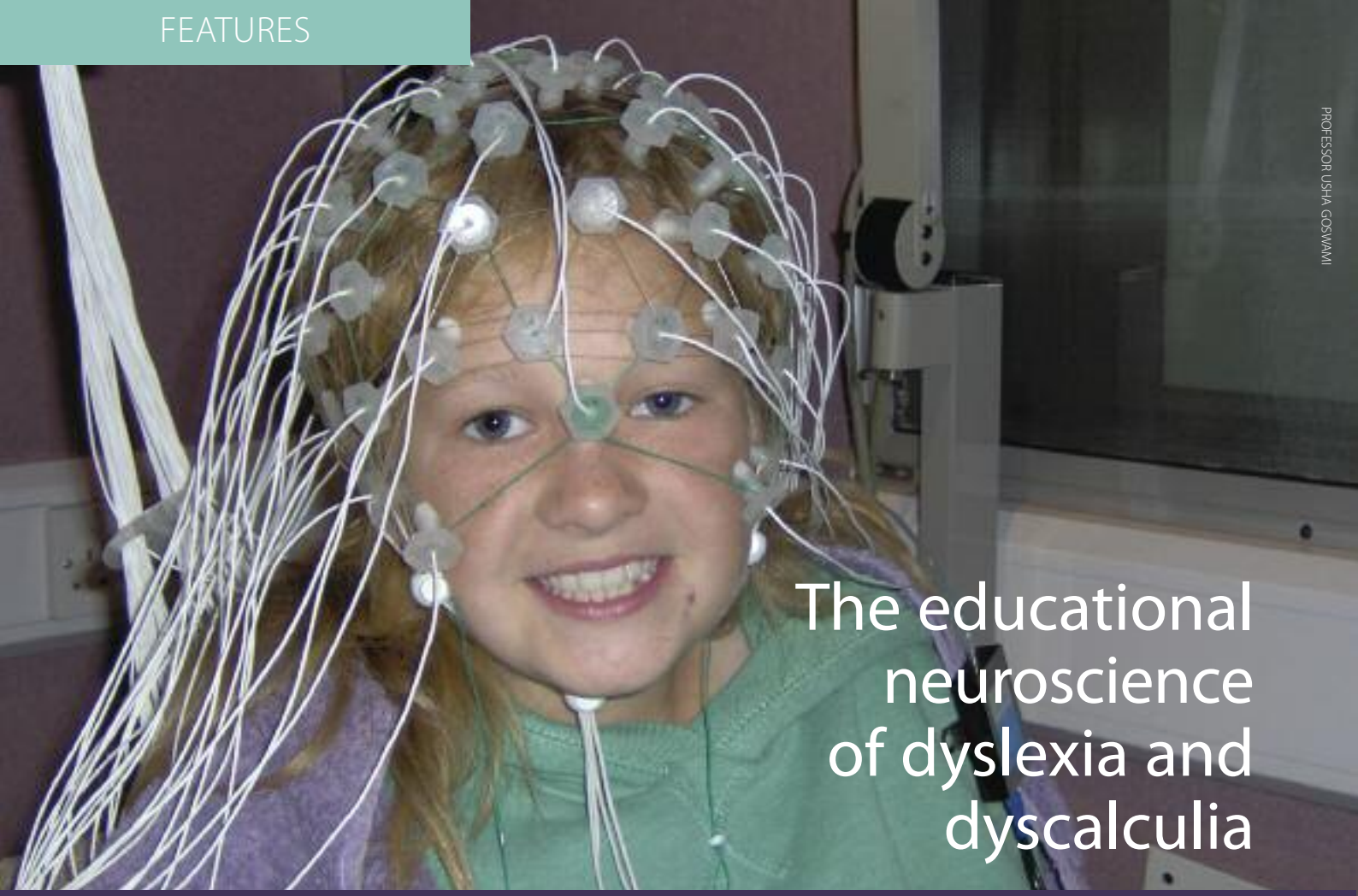
Newly funded collaborative projects on H1N1

Combating Swine Influenza (COSI) Initiative: the role of pig–pig and pig–human interactions in the development and spread of pandemic H1N1:

- epidemiological and evolutionary investigations in pigs and farm workers (**University of Cambridge**)
- immunological and dynamic modelling of infection in pigs compared with humans (**Veterinary Laboratories Agency**, Weybridge)

FluWatch: study of the transmission of pandemic H1N1 within households in England (**University College London**)

MOSAIC: study of hospitalised cases of severe infection (**Imperial College London**)



PROFESSOR USHA GOSWAMI

The educational neuroscience of dyslexia and dyscalculia

A special hairnet collects data from a young participant in the developmental dyslexia project

For some children, acquiring the important skills of learning to read or do arithmetic is fraught with difficulty. Educational neuroscience is helping to understand why.

Developmental dyslexia, which manifests as a difficulty in reading and spelling, affects about 7% of schoolchildren, mostly boys, and presents a major obstacle to educational success, future mental health and lifetime earning. Its mathematical counterpart, developmental dyscalculia, affects about 6% of schoolchildren and is found equally in boys and girls. According to figures released from the UK Government Office for Science, dyscalculia has an even higher impact on educational success than dyslexia.

Early diagnosis and appropriate educational support are known to have lasting benefits for children and adults affected by these disorders. To get this right, a better understanding is needed of how the brain acquires reading and maths skills, and the new field of educational neuroscience is helping to find the answers. In the forefront of these studies is Cambridge's Centre for Neuroscience in Education. With £2 million recent funding from the Medical Research Council (MRC), the researchers at the Centre aim to discover neural markers for dyslexia and dyscalculia through brain imaging techniques. This will enable affected children to be identified as early as possible and for targeted remediation to be delivered.

A world first

The Centre for Neuroscience in Education was the first neuroscience laboratory in the world to be established within a Faculty of Education. Launched formally in 2005, with an inaugural conference that attracted 220 teachers and educators from over 15 countries, the Centre now has a team of 24 students and researchers. Staff are trained in a variety of disciplines, spanning psychology, education, medicine, linguistics and physics. The Centre is directed by Professor Usha Goswami, with Dr Dénes Szűcs as University Lecturer in Neuroscience and Education.

From electrochemical signals to education

The main brain imaging technology used in the Centre is the electroencephalogram (EEG), a technique that can measure the voltage changes that are caused by the electrochemical activity of brain cells. Whenever a child (or adult) is thinking or feeling, tiny electrical changes occur in the brain. These changes can be measured by sensitive electrodes that are placed on the skin of the scalp, mounted in a special hairnet that enables direct recordings of brain activity to be taken. The technique is

The Centre for Neuroscience in Education team

painless, the electrodes are easy to put on and the children enjoy the measurement sessions.

But how can these electrical measurements tell us anything about the process of learning? A developmental dyslexia project is making this link by following over 100 children on a yearly basis for five years, making brain measurements at the same time as analysing speech processing, auditory processing, reading and spelling. One area of particular focus is a specific difficulty in processing the sound patterns of words, a skill called phonological awareness, which has been known for over 20 years to be the hallmark of developmental dyslexia.

The sound of syllables

Children with dyslexia find it difficult to decide whether words rhyme and to count the number of syllables in a word like *oasis*. One reason is that aspects of the auditory signal in speech are processed less efficiently by the dyslexic brain.

In a simple auditory tone task that has now been used with dyslexic children learning languages as diverse as English, Spanish, Chinese and Finnish, scientists at the Centre have shown that one particular sound parameter is more difficult to discriminate. A bit like the difference in the onset of loudness between a trumpet note and a violin note, there is a difference in the rate of onset of loudness that occurs as we produce syllables; the Cambridge researchers have found that this is impaired in developmental dyslexia. In fact, this processing difficulty means that children with dyslexia are impaired in any auditory rhythmic task – including perceiving metrical structure in music and tapping along to a beat.

Reading in rhythm

To further complicate matters, the way in which the pre-literate brain represents language is fundamentally different to the way in which the literate brain represents language. Learning to read changes the brain because learning an alphabet makes us conceptualise spoken words in terms of their spelling patterns. We automatically hear spoken language as a series of the kinds of sounds represented by letters (e.g. we hear *cat* as c + a + t); this connection between sounds and letters is called phonics. The dyslexic brain does not have the auditory distinctions efficiently in place to which phonics instruction can be easily linked.

Currently, the main remediation offered to children with developmental dyslexia is yet more intensive instruction in phonics. Instead, the research in Cambridge suggests that interventions based on rhythm and even music may be beneficial, at much earlier ages. Rhythm is more overt in music than in language, and other projects at the Centre have shown that being able to sing in time with music is predictive of syllable and rhyming skills, and that training in rhythm improves phonological awareness. Several educational interventions based on musical and speech rhythms are currently being developed at the Centre.

Magnitude of the problem

The MRC project on dyscalculia is just beginning but, here too, the neurological basis of the disorder is under scrutiny because a distinct area in the brain's parietal cortex seems to be specialised for understanding magnitude. Children with dyscalculia have enormous difficulties in making decisions about quantities, such as 'how much is four?' Intriguingly, however, scientists at the Centre have shown that the main sensory marker of magnitude difficulties – being slower to make judgements about numbers that are closer together than further apart – is not deficient in children with dyscalculia. But these children do have very poor working memories, finding it both difficult to keep relevant information in mind and to recognise mistakes.

When children start learning maths at school, changes largely occur in the language areas of the brain. The ensuing neural connections that form between memory, magnitude and decision-making processes may underlie what goes wrong in dyscalculia. This hypothesis will be explored using a variety of non-invasive imaging techniques at the Centre and in collaboration with the MRC Cognition and Brain Sciences Unit in Cambridge, in an effort to use spatial imaging technologies to deliver exact information about where the affected networks are in the brain.

With foresight

The Centre is also beginning to have an input into Government policy. Professor Goswami was the scientific co-ordinator for Learning Difficulties within the Government Office of Science 'Foresight' project on Mental Capital and Wellbeing in 2008, one of three Cambridge scientists in the lead team (along with Professors Barbara Sahakian and Felicia Huppert). If the recommendations of the Foresight project are implemented nationally, then the insights from brain science for education will eventually be reflected in the basic training of all the teachers in the country. When that happens, all University Departments of Education will need some expertise in brain science – and Cambridge will be in the vanguard once again.

Professor Usha Goswami

For more information, please contact the author, Professor Usha Goswami (ucg10@cam.ac.uk), at the Centre for Neuroscience in Education (www.educ.cam.ac.uk/centres/neuroscience/) in the Faculty of Education. **Research at the Centre is funded by grants from the MRC, Economic and Social Research Council (ESRC), European Union, Leverhulme Trust and Nuffield Foundation.**

BRITISH ACADEMY

The UK's national academy for the humanities and social sciences seeks to recognise and support leading-edge research within these fields, championing their importance and the vital role they play in raising and answering fundamental questions facing society today.

The British Academy receives £22 million in Government grant to support UK-based research and international collaboration in the humanities and social sciences. From this, over 1,000 awards are made each year, benefiting individuals based in more than 120 universities and research institutions across the UK.

Supporting research

One of the most popular British Academy funding programmes is the Postdoctoral Fellowship. These provide three-year career development opportunities to scholars such as **Dr Matilda Mroz** and **Dr Zoltán Tiba** (see panels) to develop research, teaching and publications at an early career stage. Around 45 new awards are made annually under this exceptionally competitive flagship scheme, including seven to Cambridge this year.

British Academy Research Development Awards (BARDAs) support established scholars wishing to develop a significant collaborative or individual research project. About 35 awards are made each year under this comparatively new scheme, which replaces large research fellowships and research leave. In Cambridge, BARDA-funded scholars include Dr Mandeep Dhami, who is evaluating apology in the context of restorative justice, Dr Claire Preston, who is studying 17th-century English literature and scientific investigation, and Dr Anna Williams, who is researching the architecture of theology.

The Academy also offers Small Research Grants (up to £7,500) to stimulate interdisciplinary work, collaborations or pilot studies, and several schemes focus on encouraging international collaboration, promoting capacity development and engagement. For instance, the three-year UK-Africa Academic Partnership award encourages institutional links and promotes new understandings and interchange between participating countries. In Cambridge, Dr Devon Curtis is using this award to collaborate with scholars in Uganda and Botswana on a study of rebel movements and post-conflict peace building in Africa.

The British Academy is the counterpart to the Royal Society, which supports the natural sciences. The Academy partners with the Royal Society and the Royal Academy of Engineering for the esteemed Newton International Fellowships scheme, which aims to build a global pool of research leaders and encourage long-term international collaboration.

Championing humanities and social sciences

Each year, the Academy elects 38 outstanding UK-based scholars to be Fellows of the British Academy in recognition of their research achievements. Today, there are over 900 Fellows who take a lead in representing the humanities and social sciences, and who contribute to public policy and debate. Seven Cambridge academics were among the recently elected Fellows: Professor Simon Baron-Cohen, Professor Philip Ford, Professor Jonathan Haslam, Professor Mary Jacobus, Dr John Marenbon, Professor Susan Rankin and Professor John Duncan.

Through investing in ideas, individuals and intellectual resources, the Academy aims to enhance the scholarly and cultural resources of the UK, contributing to quality of life, economic prosperity, public policy, understanding of other societies and cultural enrichment.

For more information about the British Academy, please visit www.britac.ac.uk/

Polish cinema in the frame

Cinema was a central means of cultural expression in post-war Poland. Dr Matilda Mroz is asking how and why.

'Watch them closely, for these are the last hours of their lives…,' commands the narrator at the beginning of the Polish film *Kanal* (1956), directed by Andrzej Wajda. And watching closely, frame by frame, is precisely what Dr Matilda Mroz is doing, as she examines post-war Polish films for the nuances that escaped Socialist censorship and gave cinema of the time a unique political resonance.

'Cinema is the most important art form to emerge in the 20th century,' explains Dr Mroz, from the Department of Slavonic Studies. 'In Poland, unable to communicate resistance to the Socialist regime through open political channels, oppositionists often chose to express themselves through culturally symbolic actions. Cinema became their most powerful tool, slipping subversive notions past the censors through subtle cinematic direction.'

Warsaw Uprising Memorial, Poland, on the 60th anniversary of the Uprising

Funded through a British Academy Postdoctoral Fellowship, Dr Mroz has been tracing this trend in Polish film-making, a trend that is beautifully exemplified by *Kanal*. Set among the ruins of wartime Warsaw, *Kanal* depicts the last days of the 1944 Warsaw Uprising and the attempt of the insurgents to reach another part of the city through the sewers, in which they get lost and perish.

'It was the first film that addressed the previously taboo subject of the non-Communist resistance movement, and it traumatised many viewers because it showed the soldiers escaping and then dying in the filth of the sewers rather than fighting heroically,' explains Dr Mroz. 'Even the cinematography was such that viewers often spoke of feeling as lost and claustrophobic as the characters – a marked departure from the rigorously framed films beloved of the Socialist movement.'

Understanding how cinema-goers reacted to the films is an important aspect of the research, since it affords a unique opportunity to examine the intersection between cinematic experience, historical climate and Polish culture. Dr Mroz's funding enabled her to travel to Warsaw to the National Film Archives last year, where she made a lucky discovery: 'Sixty years ago, someone had diligently cut out every article and mention of the very films that I was interested in and pasted them into scrapbooks. There's something very exciting about opening these yellowing, crinkled books and thinking about the archivists determined to preserve for posterity both the 'official' and the controversial responses to important films.' Now, decades later, Dr Mroz is rediscovering these invaluable records and their testimony to the enduring power of cinema for the Polish people.

DR MATILDA MROZ

Dr Matilda Mroz

For more information, please contact Dr Matilda Mroz (mm570@cam.ac.uk) at the Department of Slavonic Studies (www.mml.cam.ac.uk/slavonic/).

DR ZOLTÁN TIBA

Children in Namasalima village, Malawi, eating maize porridge

Famine's changing face

Dr Zoltán Tiba's research on why famines happen is posing questions about the root causes and possible long-term interventions.

'The nature of famine has changed,' said Dr Zoltán Tiba, a British-Academy-funded Postdoctoral Fellow in the Centre of African Studies. 'Today, famines happen not just because there is a decline in the availability or in the access to food, but because of factors such as the political economy and the toll of HIV-AIDS on the working population.'

Dr Tiba's research has set out to develop fresh analytical tools to understand famines. He takes Malawi in sub-Saharan Africa as his primary focus. 'Malawi is an interesting case since in many ways it challenges commonly accepted views about the causes of famine. The famine in 2002 demonstrated that democracy does not always 'end famine'. Contemporary famines have multiple and complex causes, and traditional interventions such as food aid distributions are not necessarily the best solution to 'new' famines.'

For the past seven years, Dr Tiba has been conducting research in a Malawian village, where he has been interviewing villagers and carrying out household surveys, as well as speaking to government officials and aid agencies. His findings are building a unique picture of village life and the Malawians' experiences of food insecurity. 'The area is a Garden of Eden, with lush vegetation and plenty of water and, yet, chronic food insecurity is a serious problem and the threat of famines is still evident.'

'Increasingly my research is emphasising the role of local attitudes to diversification of diet and production,' explained Dr Tiba. 'One possibility for long-term change at the macro level is to focus on the micro level – something as simple as individuals growing fruits and raising small livestock in addition to growing cereals would add to the safety net to subvert chronic food insecurity and famines in a country like Malawi.'

Dr Zoltán Tiba

For more information, please contact Dr Zoltán Tiba (zt214@cam.ac.uk) at the Centre of African Studies (www.african.cam.ac.uk/).

Professor Jaideep Prabhu

Jaideep Prabhu is the first Jawaharlal Nehru Professor of Indian Business and Enterprise, which was endowed by the Government of India, and is Director of the Centre for India & Global Business at Judge Business School. With a passion for understanding and promoting India's place in shaping the global knowledge economy, he leads an important component of the University's long-standing partnership with India.

'In two decades' time, the expectation is that India will have one of the world's largest economies – a result of its escalating engagement with innovation, its service economy and its young and dynamic population,' explained Professor Prabhu. 'It's an incredibly exciting time to be looking at the nation's role in the global economy, both through the lens of innovation and from a systematic business perspective.'

The Centre for India & Global Business, launched in March 2009 with start-up funds donated by the BP Group, has an overarching research theme of innovation and the role that it can play in India. This stretches from how and why the world's largest multinationals are increasingly locating their global R&D and innovation activities in India, how Indian firms themselves are internationalising and increasing their global competitiveness, to how organisations are actively innovating with those in India who live below the poverty line to make their lives better.

Professor Prabhu brings to the Centre his extensive research experience gained in the USA, Europe and the UK. As Director, his goal is to create a collaborative platform that draws in multiple stakeholders from India, the UK and other countries. 'It's not just the research that counts, it's also how we promote and guide engagement with innovation in India and, for this, the role of other stakeholders will be crucial,' he explained. 'By understanding some of the challenges that lie ahead, we can help to derive solutions that will be of widespread benefit to the global economy.'

What would others be surprised to learn about you?
When I was younger, I was obsessed with fiction and poetry. I was particularly fond of the poetry of Auden, Brodsky and Walcott, and the novels of Saul Bellow. I read widely and went around with all these literary thoughts in my head, imagining that one day I might be a poet. Although I took a more conventional route and ended up studying engineering and business, I'm still fascinated by the written word.

Have you ever had a Eureka moment?
I've had moments of dawning realisation that have had a profound influence on me. Probably the most significant of these was after moving from India to the US to study at the University of Southern California in the early 1990s. I was swept away by the intellectual openness and I considered switching from engineering to philosophy. I also saw at first hand how differently to India the US operated in terms of the role of the state versus free enterprise. It was my first introduction to the complexities underlying political economies worldwide.

What's the best piece of advice you've ever been given?
When I was wrestling with whether to embark on a philosophy doctorate, my uncle (himself a philosopher) suggested that I choose business instead. Deciding against philosophy was very hard to accept then, but, as it turns out, he was absolutely right. I had grown up questioning why there is inequality in society, in particular why some people and countries are wealthy and others are not. Studying business has given me the tools to think about these questions systematically. I like the fact that business engages with the world and its social and economic prospects, and the fact that there are constantly new questions to ask and diverse theories and methods to use to find answers to them.

What motivates you to go to work each day?
The idea that something I do might in some small way make a difference to people's lives. One aspect of the Centre's research is looking at how business can help improve the lives of people who live on under $2 a day – about 2.5 billion people around the world, many of whom are in India. If you think about innovation as the shaping of technology to deliver new benefits for people, then even the most basic innovations will improve lives,

provided a business solution can be found to make them viable. Even something as basic as using a mobile phone as a micro-payment system can open up enormous opportunities in a country like India, where 60% of the population has no bank account and, as such, remains outside the formal economy.

What's your favourite research tool?
It has to be statistics, both conceptually and as a practical, computer-based tool. Without statistics it is very hard to do any kind of systematic social science.

What will the future look like in 2050?
The emerging markets will have emerged. Nations like India and China, as well as Russia, Brazil and countries in Latin America and Africa, will all have a bigger role to play on the global stage. There will be greater movement of people, more diversity at work, increased democracy, and essentially a more connected world. With climate change and population growth, we'll face significant challenges, especially scarcity in energy, food and water. But necessity is the mother of invention and it is my belief that we will see some significant entrepreneurial and business solutions to the challenges ahead.

Forthcoming events: Save the dates!

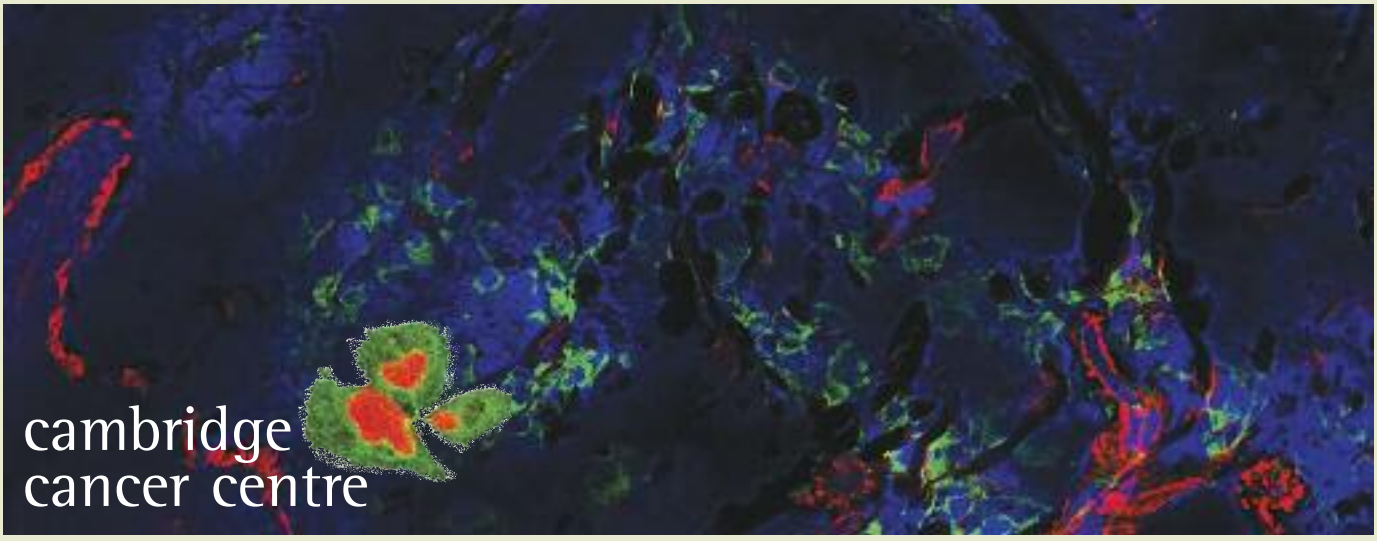
TOP RIGHT: NIGEL LUCKHURST; ALL OTHERS: ELLA WOOLER

8–21 March 2010

Cambridge Science Festival: 'Diverse Science'

Join us for the UK's largest free science festival, exploring subjects from astronomy to zoology, with demonstrations, hands-on experiments, talks from leading scientists, and visits to University and partner facilities. Over 180 events will be on offer, designed to give families, adults and children hands-on science and insight into the University's cutting-edge scientific research. Many of the activities, demonstrations and children's lectures will take place on Science on Saturdays (13 and 20 March).

The theme will be 'Diverse Science' to celebrate the International Year of Biodiversity in 2010. There will be many opportunities to delve into diversity at events for all ages during our family fun days and adult evening lecture series. Highlights for adults include lectures by Professor David Spiegelhalter (the Winton Professor of the Public Understanding of Risk) and a panel discussion entitled 'What price nature' organised in conjunction with the Cambridge Conservation Initiative. Highlights for children include an hour of explosive demonstrations with the Naked Scientists, and a Food Factory Workshop – where you're the chef with the Medical Research Council Human Nutrition Research Unit. The full programme is available from www.cambridgescience.org/ from January 2010.



STEPHEN GOLDIE

25 June 2010

Cambridge Cancer Centre Symposium
Cancer Research UK Cambridge Research Institute, Li Ka Shing Centre, Cambridge

The Cambridge Cancer Centre (CCC) Symposium is a one-day event highlighting the interdisciplinary and collaborative cancer research being carried out in Cambridge. This is the fourth CCC Symposium to take place.

Talks from invited speakers and from recipients of CCC pilot project funding in 2009 will showcase the latest interdisciplinary cancer research undertaken in Cambridge. There will be a Keynote Lecture by Professor Mariano Barbacid of the Centro Nacional de Investigaciones Oncológicas in Madrid. The day will have ample opportunity for networking during the poster session and barbecue, with delegates from University departments, institutes and local biotech companies. The full programme will be available in spring 2010 and registration will open shortly after this time on the CCC website (www.cancer.cam.ac.uk/). For more information, please email katrien.vanlook@cancer. org.uk

Your way into Cambridge

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